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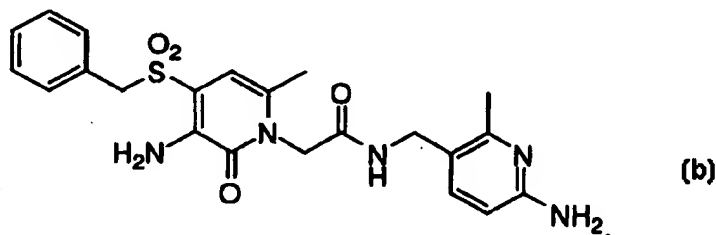
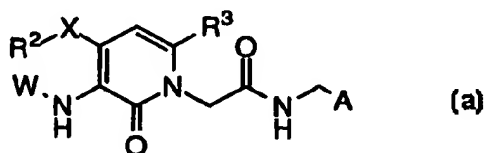


16

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<p>(21) International Application Number: PCT/US98/00875</p> <p>(22) International Filing Date: 16 January 1998 (16.01.98)</p> <p>(30) Priority Data: 60/036,149 22 January 1997 (22.01.97) US 9704209.7 28 February 1997 (28.02.97) GB</p> <p>(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SANDERSON, Philip, E. [GB/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). LYLE, Terry, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). COBURN, Craig [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p>	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	

(54) Title: THROMBIN INHIBITORS



(57) Abstract

A compound which inhibits human thrombin and where has structure (a) such as (b).

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TITLE OF THE INVENTION

THROMBIN INHIBITORS

BACKGROUND OF THE INVENTION

5 Thrombin is a serine protease present in blood plasma in the form of a precursor, prothrombin. Thrombin plays a central role in the mechanism of blood coagulation by converting the solution plasma protein, fibrinogen, into insoluble fibrin.

 Edwards *et al.*, *J. Amer. Chem. Soc.* (1992) vol. 114, pp.
10 1854-63, describes peptidyl α -ketobenzoxazoles which are reversible inhibitors of the serine proteases human leukocyte elastase and porcine pancreatic elastase.

 European Publication 363 284 describes analogs of peptidase substrates in which the nitrogen atom of the scissile amide group of the
15 substrate peptide has been replaced by hydrogen or a substituted carbonyl moiety.

 Australian Publication 86245677 also describes peptidase inhibitors having an activated electrophilic ketone moiety such as fluoromethylene ketone or α -keto carboxyl derivatives.

20 Thrombin inhibitors described in prior publications contain sidechains of arginine and lysine. These structures show low selectivity for thrombin over other trypsin-like enzymes. Some of them show toxicity of hypotension and liver toxicity.

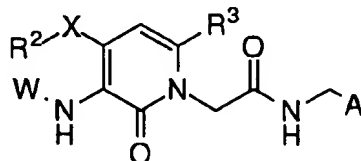
 European Publication 601 459 describes sulfonamido
25 heterocyclic thrombin inhibitors, such as N-[4-[(aminoimino-methyl)amino]butyl]-1-[N-(2-naphthalenylsulfonyl)-L-phenylalanyl]-L-prolinamide.

 WO 94/29336 describes compounds which are useful as thrombin inhibitors.

30 WO 96/18644 describes heterocyclic derivatives as thrombin inhibitors.

SUMMARY OF THE INVENTION

The invention relates to compounds of the formula:



wherein

5 W is

hydrogen,

R¹-,

R¹OC(O)-,

R¹C(O)-,

10 R¹SO₂-,

(R¹)_m(CH₂)_nNHqC(O)-,

where n is 0-4, m is 1 or 2, wherein R¹ is same or different, and
q is 0 or 1, with the proviso that where n is 1-4, q is 1 and m is 1,
and where n is 0, m is 1 or 2, and q is 0 or 1, and where n is 0,
15 m is 2 and q is 0;

R¹ is

R¹⁷(CH₂)_t-, where t is 0-4;

(R¹⁷)(OR¹⁷)CH(CH₂)_p-, where p is 1-4,

20 (R¹⁷)₂CH(CH₂)_r-, where r is 0-4 and each R¹⁷ can be the same or
different, and wherein (R¹⁷)₂ can also form a ring with CH
represented by C₃-7 cycloalkyl, C₇-12 bicyclic alkyl, C₁₀-16
tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic
heterocyclic ring which can be saturated or unsaturated, and
25 which contains from one to three heteroatoms selected from
the group consisting of N, O and S,

R¹⁷O(CH₂)_p-, wherein p is 1-4;

R², R¹⁴ and R¹⁷ are independently selected from

30 -phenyl, unsubstituted or substituted with one or more of

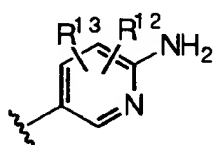
5 C₁₋₄ alkyl,
C₁₋₄ alkoxy,
halogen,
hydroxy,
COOH, or
CONH₂,
naphthyl,
biphenyl,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
10 heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
-C₁₋₇ alkyl, unsubstituted or substituted with one or more of
hydroxy,
15 COOH,
amino,
aryl,
C₃₋₇ cycloalkyl,
heteroaryl, or
20 heterocycloalkyl,
-CF₃
C₃₋₇ cycloalkyl,
C₇₋₁₂ bicyclic alkyl, or
C₁₀₋₁₆ tricyclic alkyl;
25
X is
CF₂,
CR¹⁵₁₅,R¹⁶₁₆
30 wherein R¹⁵ and R¹⁶ are independently
hydrogen,
C₃₋₇ cycloalkyl,
C₁₋₄ alkyl unsubstituted or substituted with one or more of
hydroxy,
35 COOH,

amino,
 aryl,
 heteroaryl, or
 heterocycloalkyl,
 5 aryl,
 heteroaryl,
 heterocycloalkyl, or
 R¹⁵ and R¹⁶ are joined to form a four to seven
 membered cycloalkyl ring unsubstituted or
 10 substituted with hydroxy, amino or aryl, or

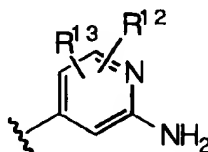
S(O)_r, where r is 0-2;

R³ is
 15 hydrogen,
 C₁₋₄ alkyl,
 C₃₋₇ cycloalkyl, or
 trifluoromethyl;

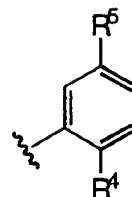
20 A is chosen from one of the following radicals:



II



III



IV

with the proviso that when A is radical IV, R²-X is not C₁₋₄ alkyl,
 C₃₋₇ cycloalkyl, or trifluoromethyl;

25 R⁴ is
 hydrogen,

C₁₋₄ alkyl,

- C₁₋₄ alkoxy,
halogen,
-OCH₂CF₃,
-COOH,
5 -OH,
-COOR⁶, where R⁶ is C₁₋₄alkyl,
-CONR⁷R⁸, where R⁷ and R⁸ are independently
hydrogen or C₁₋₄alkyl,
-(CH₂)₁₋₄OH,
10 -CH₂NHC(O)CH₃,
-CH₂NHC(O)CF₃,
-CH₂NHSO₂CH₃,
-SO₂NH₂,
-(CH₂)₁₋₄SO₂NR⁷R⁸,
15 -(CH₂)₁₋₄SO₂R⁶,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
20 -ZCH₂CO₂H,
-ZCH₂CO₂CH₃,
-ZCH₂R¹⁴,
-ZCH₂CO₂(CH₂)₁₋₃CH₃,
-Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,
25 wherein
R⁹ is H or C₁₋₄ alkyl,
R¹⁰ and R¹¹ are independently
hydrogen,
C₃₋₇ cycloalkyl,
30 aryl,
heteroaryl,
heterocycloalkyl,
C₁₋₄ alkyl unsubstituted or substituted with one or more of
hydroxy,
35 COOH,

amino,
aryl,
heteroaryl, or
heterocycloalkyl, or

5 R¹⁰ and R¹¹ are joined to form a four to seven
membered cycloalkyl ring unsubstituted or
substituted with hydroxy, amino or aryl,

wherein Z is O, S or CH₂;

10

R⁵ is

hydrogen,
halogen,
C₁₋₄ alkyl,
15 C₁₋₄ alkoxy,
CN, or
CO₂NH₂; and

R¹² and R¹³ are independently

20

hydrogen,
C₁₋₄ linear or branched alkyl or alkoxy,
C₃₋₇ cycloalkyl,
halogen, or
trifluoromethyl;

25

and pharmaceutically acceptable salts thereof.

The invention includes a composition for inhibiting loss of
blood platelets, inhibiting formation of blood platelet aggregates,
30 inhibiting formation of fibrin, inhibiting thrombus formation, and
inhibiting embolus formation in a mammal, comprising a compound of
the invention in a pharmaceutically acceptable carrier. These
compositions may optionally include anticoagulants, antiplatelet agents,
and thrombolytic agents. The compositions can be added to blood, blood

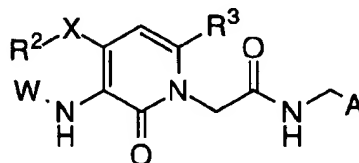
products, or mammalian organs in order to effect the desired inhibitions.

5 The invention also includes a composition for preventing or treating atrial fibrillation, deep venous thrombosis, pulmonary embolism, cardiac thromboembolism and associated stroke in patients with atrial fibrillation, mechanical heart valves, or recent myocardial infarction with decreased left ventricular function, disseminated intravascular coagulation, ocular build up of fibrin, unstable angina, refractory angina, transient ischemic attacks, thrombotic stroke, 10 embolic stroke, and reocclusion or restenosis of recanalized vessels, in a mammal, comprising a compound of the invention in a pharmaceutically acceptable carrier. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents.

15 The invention also includes a method for reducing the thrombogenicity of a surface in a mammal by attaching to the surface, either covalently or noncovalently, a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

A class of these compounds is



wherein

5 W is

- hydrogen,
- C₁₋₄ alkyl,
- C₃₋₇cycloalkyl,
- SO₂C₁₋₇ alkyl, or
- 10 -(CH₂)_nCOOH, where n is 1-4;

R² is

- C₁₋₇ alkyl
- 15 -(CH₂)_u-C₃₋₇cycloalkyl, wherein u is 0, 1, or 2,
- (CH₂)_u-phenyl, wherein phenyl is unsubstituted or substituted with one or more of the moieties selected from the group consisting of
- C₁₋₄ alkyl,
- 20 C₁₋₄ alkoxy,
- halogen,
- hydroxy,
- COOH, or
- CONH₂
- 25 wherein u is 0, 1, or 2,
- 2-thienyl, or
- 3-thienyl;

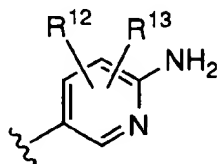
X is

- S-, -SO₂-, or CH₂;
- 30

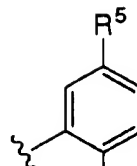
\mathbb{R}^3 is

C₁₋₄ linear alkyl;

A is chosen from one of the following radicals:



or



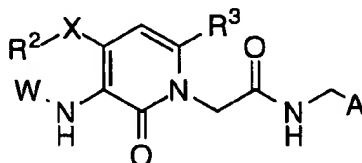
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IV

with the proviso that when A is radical IV, R²-X- is not C₁₋₄ alkyl,

and pharmaceutically acceptable salts thereof.

A group of this class of compounds is



wherein

W is

hydrogen,

-SO₂CH₃, or

-CH₃,

$$-\text{CH}_2\text{COOH};$$

R² is

 $-\text{CH}_3,$

-(CH₂)_u-C₃₋₆cycloalkyl, wherein u is 0 or 1;

-(CH₂)_u-phenyl, wherein u is 0 or 1,

$$-\text{CH}_2\text{C}(\text{CH}_3)_3,$$
$$-\text{CH}(\text{CH}_3)_2,$$

-phenyl-CH₃,

-2-thienyl, or

-3-thienyl;

5 X is

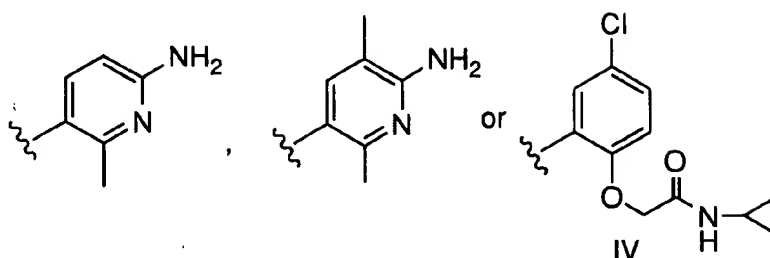
-S-, -SO₂-, or CH₂;

R³ is

-CH₃;

10

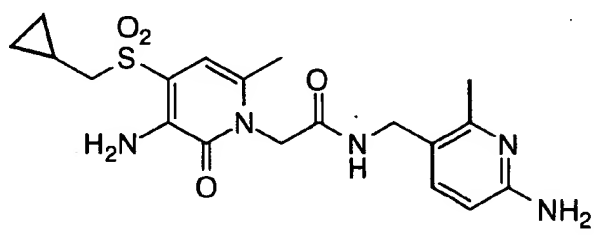
A is chosen from one of the following radicals:

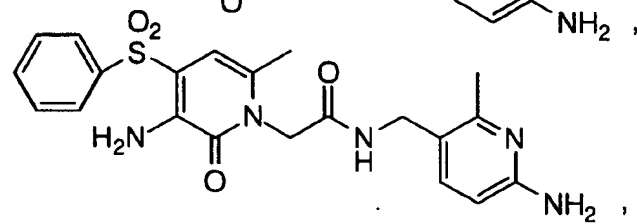
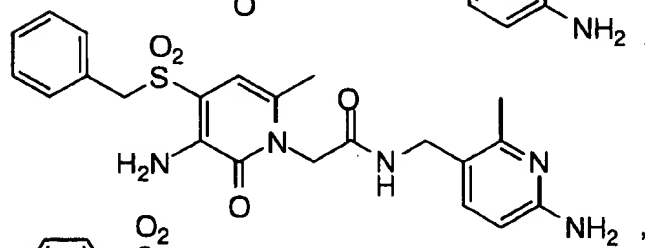
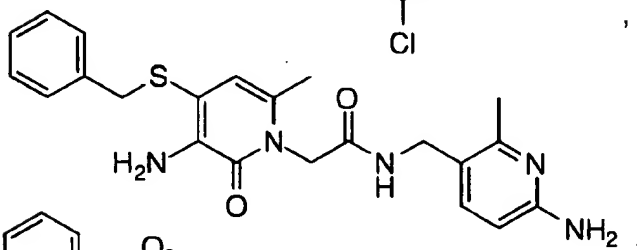
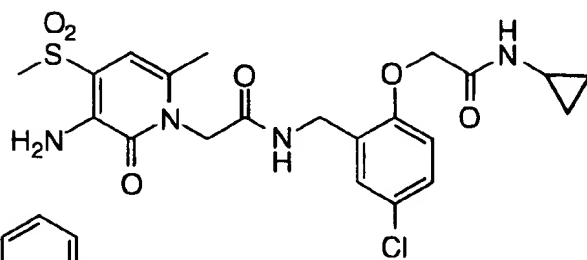
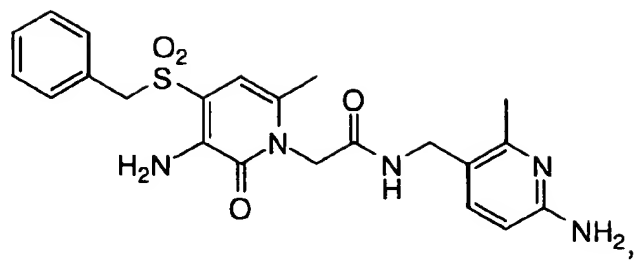


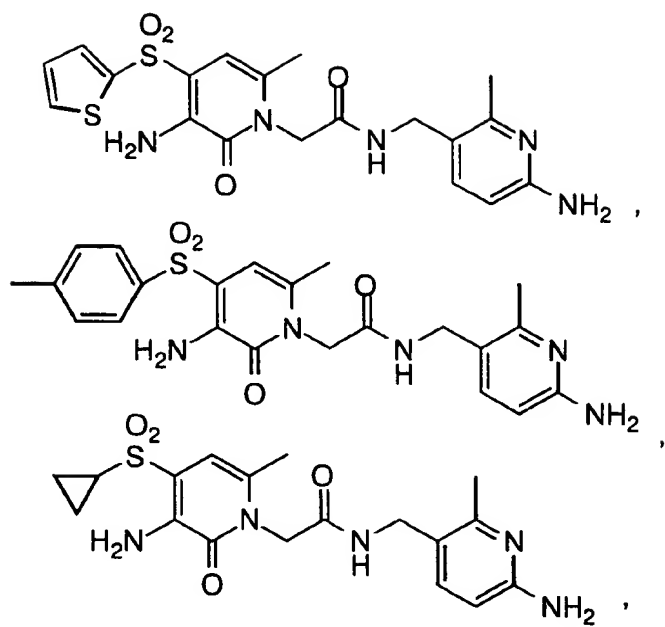
with the proviso that when A is radical IV, R²-X- is not C₁₋₄ alkyl,

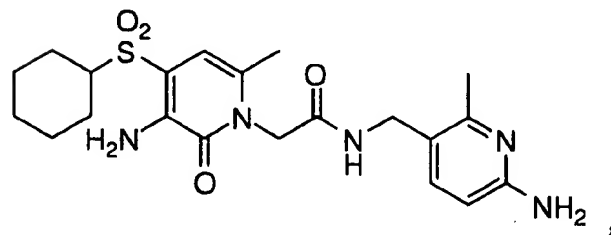
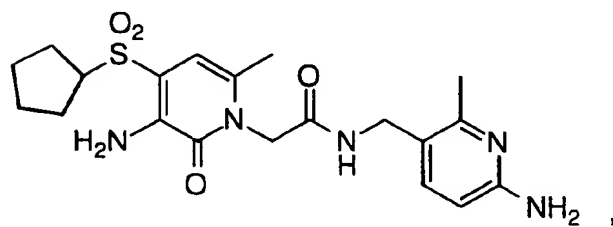
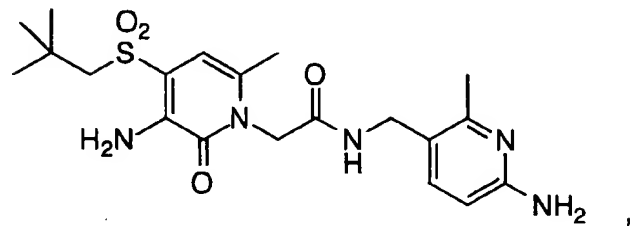
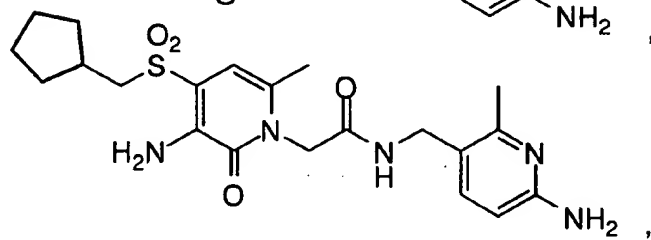
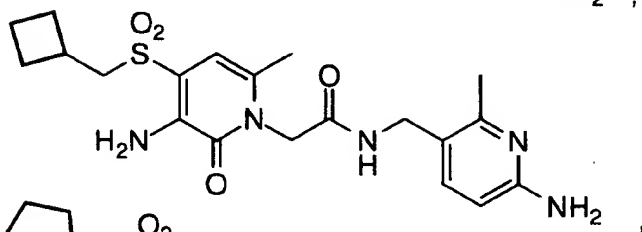
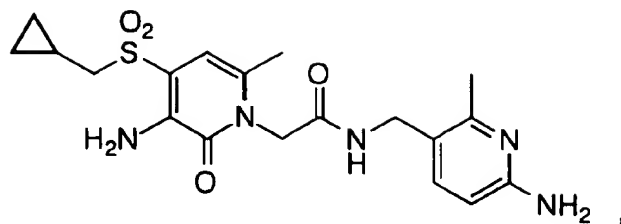
15 and pharmaceutically acceptable salts thereof.

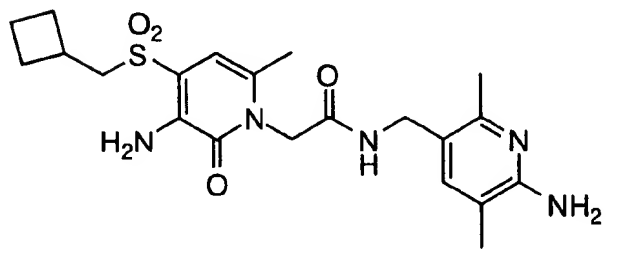
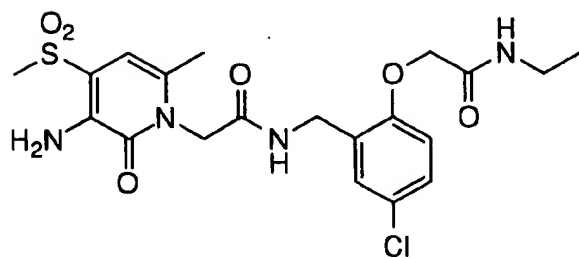
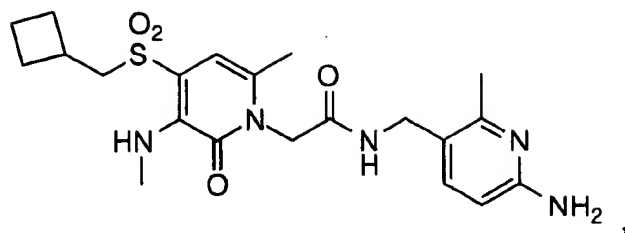
Specific embodiments of this group are



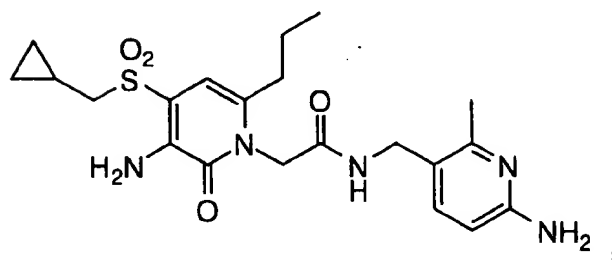


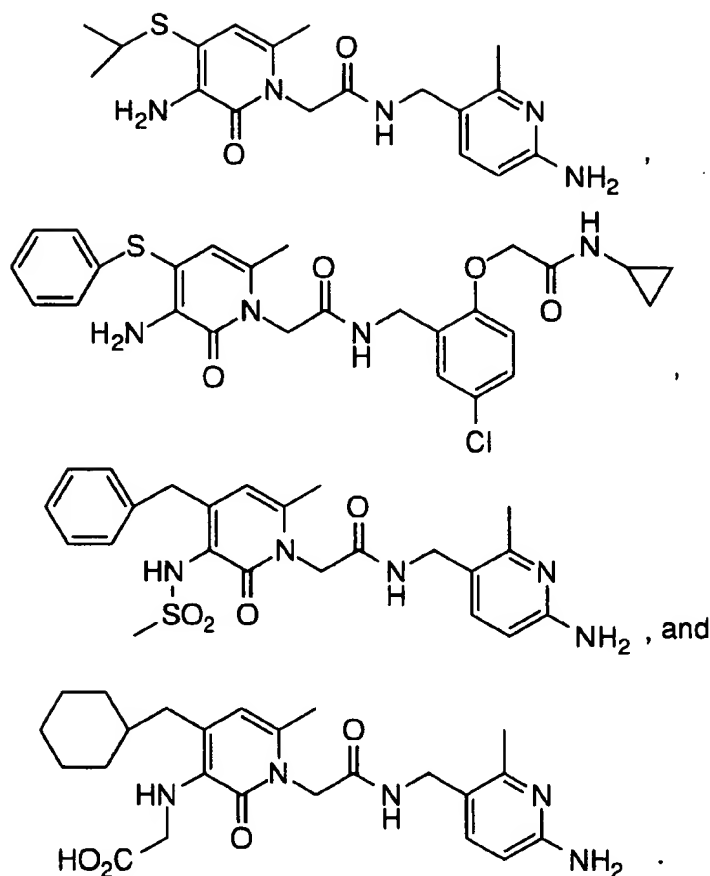






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Compounds of the present invention, which are thrombin inhibitors, are useful in anticoagulant therapy. Anticoagulant therapy is indicated for the treatment and prevention of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, dogs, cats, rats, and mice.

Thrombin inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, thrombin inhibitors can

be added to or contacted with any medium containing or suspected of containing thrombin and in which it is desired that blood coagulation be inhibited, e.g. when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems

The compounds of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent. For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The compounds can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or

polyethyleneoxide-polylysine substituted with palmitoyl residues.

Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and

5 polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, 10 sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, 15 or arrest the progress of the condition.

Oral dosages of the compounds, when used for the indicated effects, will range between about 0.001 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 0.01-100 mg/kg/day and most preferably 0.1-20 mg/kg/day. Intravenously, the most 20 preferred doses will range from about 0.001 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, the thrombin inhibitors may be administered in divided doses of two, three, or four times daily. Furthermore, they can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, 25 using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

For example, oral tablets can be prepared which contain an 30 amount of active compound of between 1 and 500 mg, e.g. 1, 10, 100, 200, 300, 400 or 500 mg. Typically, a patient in need of thrombin inhibitor compound, depending on weight and metabolism of the patient, would be administered between about 20 and 500 mg active compound per day. For a patient requiring 500 mg per day, two tablets containing 125 mg of 35 active compound can be administered in the morning and two tablets

containing 125 mg of active compound can again be administered in the evening. For a patient requiring 200 mg per day, one tablet containing 100 mg of active compound can be administered in the morning and one tablet containing 100 mg of active compound can again be administered
5 in the evening. For patient requiring 10 mg per day, one tablet containing 5 mg of active compound can be administered in the morning and one tablet containing 5 mg of active compound can again be administered in the evening.

An i.v. formulation can be administered to patients
10 requiring parenteral administration, such as hospitalized patients who are fasted (e.g. perioperative patients) and certain patients with indwelling catheters. For example, an i.v. formulation having 100 mg/ml active ingredient, at pH 4, could be administered twice a day at a dose of 0.5 ml/kg.

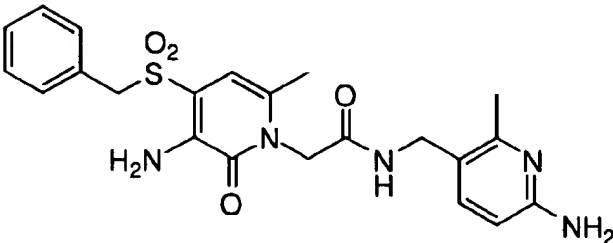
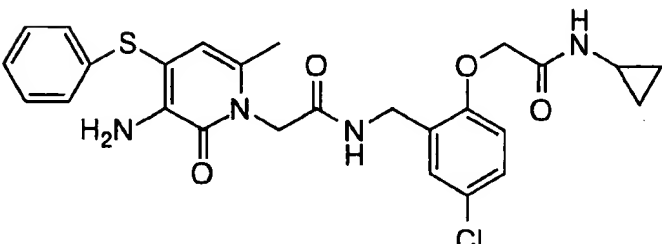
15 The compounds are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the
20 like, and consistent with convention pharmaceutical practices.

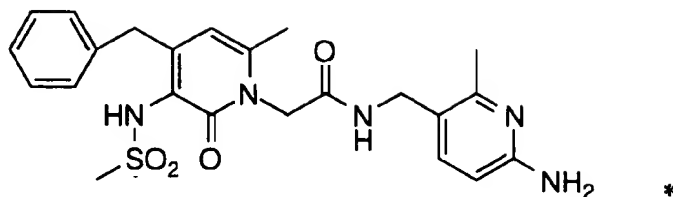
For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate,
25 dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents
30 and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms
35 include sodium oleate, sodium stearate, magnesium stearate, sodium

benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds can also be co-administered with suitable
 5 anti-coagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various ascular pathologies. For example, the compounds enhance the efficiency of tissue plasminogen activator-mediated thrombolytic
 10 reperfusion. The compounds may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter. They may also be combined with heparin, aspirin, or warfarin.

Compounds of the invention are shown in the table below. These compounds inhibit thrombin with the following potency according
 15 to in vitro measurements:

Structure	thrombin Ki (nM)
	* > 10 ** < 10
	**
	**



In vitro assay for determining proteinase inhibition

5 Assays of human α -thrombin and human trypsin were performed at 25°C in 0.05 M TRIS buffer pH 7.4, 0.15 M NaCl, 0.1% PEG. Trypsin assays also contained 1 mM CaCl_2 .

 In assays wherein rates of hydrolysis of a *p*-nitroanilide (pna) substrate were determined, a Thermomax 96-well plate reader
10 was used to measure (at 405 nm) the time dependent appearance of *p*-nitroaniline. sar-PR-pna (sarcosine-Pro-Arg-*p*-nitroanilide) was used to assay human α -thrombin ($K_M=125 \mu\text{M}$) and human trypsin ($K_M=59 \mu\text{M}$). *p*-Nitroanilide substrate concentration was determined from measurements of absorbance at 342 nm using an extinction coefficient of
15 $8270 \text{ cm}^{-1}\text{M}^{-1}$.

 In certain studies with potent inhibitors ($K_i < 10 \text{ nM}$) where the degree of inhibition of thrombin was high, a more sensitive activity assay was employed. In this assay the rate of thrombin catalyzed hydrolysis of the fluorogenic substrate Z-GPR-afc (Cbz-Gly-Pro-Arg-7-amino-4-trifluoromethyl coumarin) ($K_M=27 \mu\text{M}$) was determined from
20 the increase in fluorescence at 500 nm (excitation at 400 nm) associated with production of 7-amino-4-trifluoromethyl coumarin. Concentrations of stock solutions of Z-GPR-afc were determined from measurements of absorbance at 380 nm of the 7-amino-4-trifluoromethyl coumarin
25 produced upon complete hydrolysis of an aliquot of the stock solution by thrombin.

 Activity assays were performed by diluting a stock solution of substrate at least tenfold to a final concentration $\leq 0.5 K_M$ into a solution containing enzyme or enzyme equilibrated with inhibitor.
30 Times required to achieve equilibration between enzyme and inhibitor

were determined in control experiments. Initial velocities of product formation in the absence (V_0) or presence of inhibitor (V_i) were measured. Assuming competitive inhibition, and that unity is negligible compared $K_m/[S]$, $[I]/e$, and $[I]/e$ (where $[S]$, $[I]$, and e respectively represent the total concentrations, of substrate, inhibitor and enzyme), the equilibrium constant (K_i) for dissociation of the inhibitor from the enzyme can be obtained from the dependence of V_0/V_i on $[I]$ shown in equation 1.

$$V_0/V_i = 1 + [I]/K_i \quad (1)$$

The activities shown by this assay indicate that the compounds of the invention are therapeutically useful for treating various conditions in patients suffering from unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, and reocclusion or restenosis of recanalized vessels.

Some abbreviations that may appear in this application are as follows.

Designation

BOC (Boc)	t-butyloxycarbonyl
HBT(HOBT or HOBt)	1-hydroxybenzotriazole hydrate
BBC reagent	benzotriazolyloxy-bis(pyrrolidino)-carbonium hexafluorophosphate
PyCIU	1,1,3,3-bis(tetramethylene)-chlorouronium hexafluorophosphate
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
(BOC) ₂ O	di-t-butyl dicarbonate
DMF	dimethylformamide
Et ₃ N or TEA	triethylamine
EtOAc	ethyl acetate
TFA	trifluoroacetic acid

	DMAP	dimethylaminopyridine
	DME	dimethoxyethane
	BH ₃ -THF	Borane-tetrahydrofuran complex
	D-Phe(3,4-Cl ₂)	D-3,4-Dichlorophenylalanine
5	D-3,3-dicha	D-3,3-Dicyclohexylalanine
	Pro	Proline
	Arg	Arginine
	Gly	Glycine
	D-3,3,-diphe	D-3,3-Diphenylalanine
10	LAH	lithium aluminum hydroxide
	Cy	cyclohexyl
	POCl ₃	phosphorous oxychloride
	MeCN	acetonitrile
	BnEt ₃ N ⁺ Cl ⁻	benzyl triethyl ammonium chloride
15	NaH	sodium hydride
	DMF	dimethylformamide
	BrCH ₂ COO ^t Bu	tert butyl bromoacetate
	EtOH	ethyl alcohol
	Pd(C)	palladium on activated carbon catalyst
20	CF ₃ COOH	trifluoroacetic acid
	DCM	dichloromethane
	DIPEA	diisopropylethylamine

25 The compounds of the present invention may have chiral centers and occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention.

30 The term "alkyl" means straight or branched alkane containing 1 to about 10 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexy, octyl radicals and the like. The term "alkenyl" means straight or branched alkene containing 2 to about 10 carbon atoms, e.g., propylenyl, buten-1-yl, isobutenyl, pentylen-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl radicals and the
35 like. The term "alkynyl" means straight or branched alkyne containing

2 to about 10 carbon atoms, e.g., ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like. Cycloalkyl means a cyclic, saturated ring containing 3 to 8 carbon atoms, e.g.,
5 cyclopropyl, cyclohexyl, etc. Halogen means chloro, bromo, fluoro or iodo. The term "aryl" means a 5- or 6-membered aromatic ring containing 0, 1, or 2 heteroatoms selected from O, N, and S, e.g. phenyl, pyridine, pyrimidine, imidazole, thiophene, oxazole, isoxazole, thiazole, and amino- and halogen- substituted derivatives thereof.

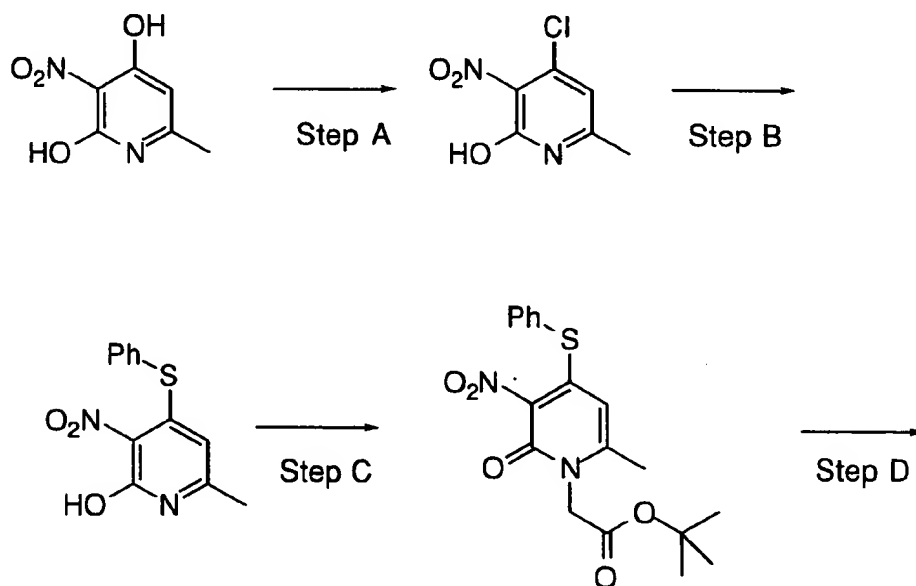
10 The pharmaceutically-acceptable salts of the compounds of the invention (in the form of water- or oil-soluble or dispersible products) include the conventional non-toxic salts or the quaternary ammonium salts which are formed, e.g., from inorganic or organic acids or bases. Examples of such acid addition salts include acetate, adipate, alginate,
15 aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate,
20 methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, and undecanoate. Base salts include ammonium salts, alkali metal salts such as sodium and potassium salts, alkaline earth metal salts such as calcium and
25 magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides;
30 dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides and others.

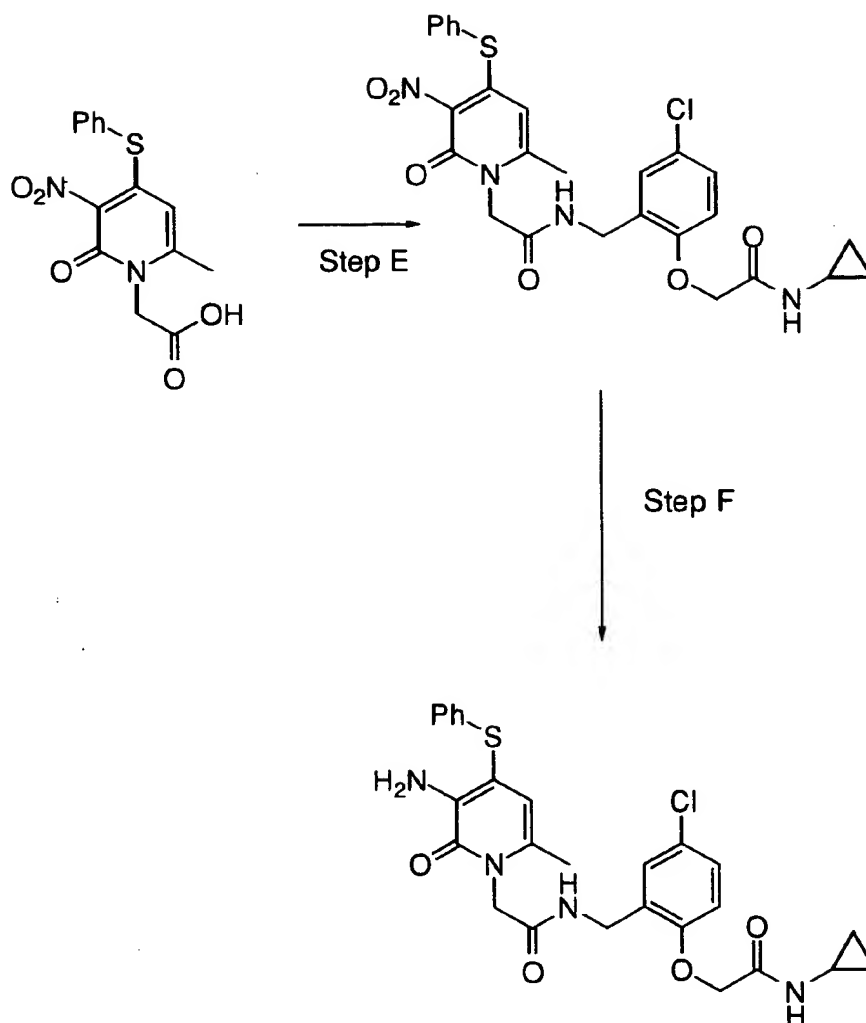
Unless otherwise stated, all NMR determinations were
35 made using 400 MHz field strength.

The compounds of the present invention, where X is S(O)_r, may be prepared using METHODS 1-5:

METHOD 1 (as exemplified by Example II)

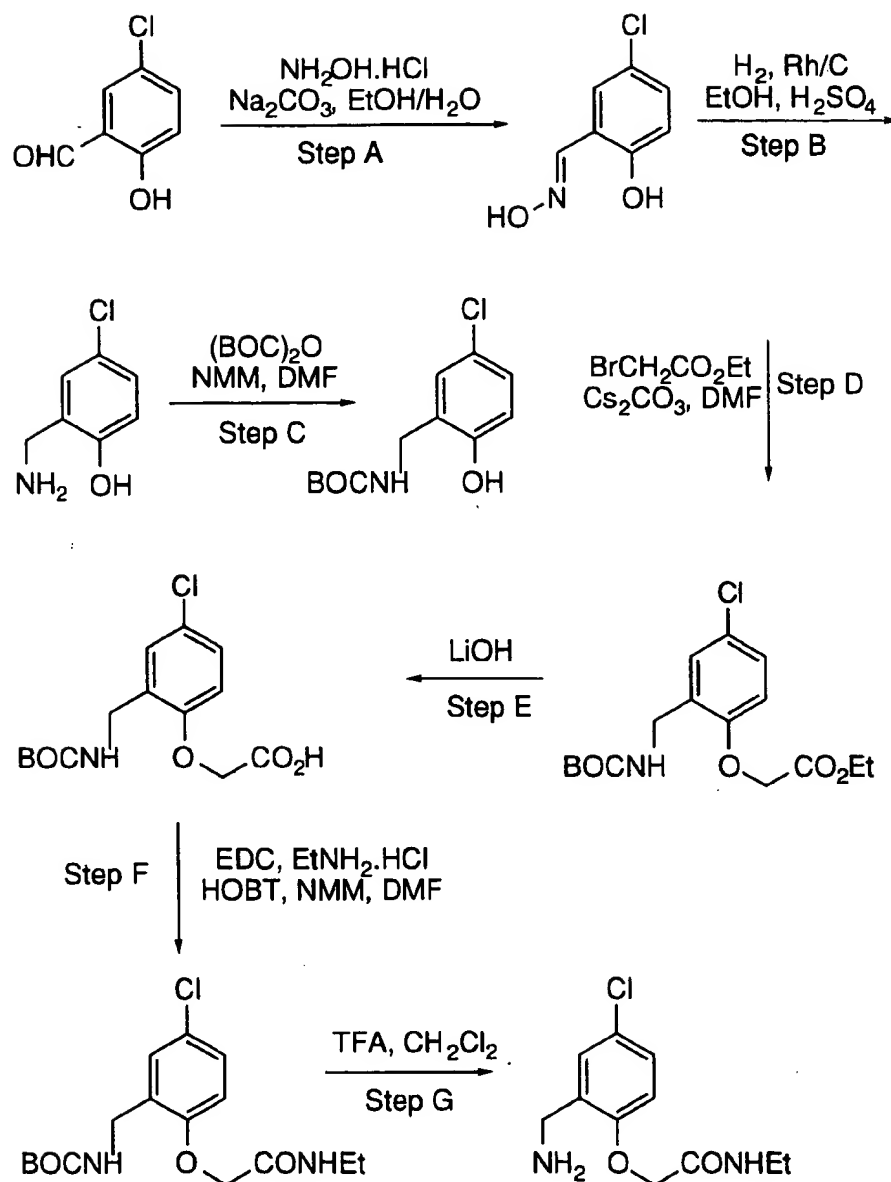
- 5 Starting 2,4-dihydroxy-3-nitropyridine is reacted with a dehydrating chloride source, for example phosphorous oxychloride, in Step A to give the 4-chloropyridine. This is reacted in Step B with a thiol in the presence of a base such as triethylamine, and is then alkylated in Step C with an acetate equivalent such as t-butylbromoacetate. The ester may be deprotected by a strong acid such as TFA in Step D and the resulting carboxylic acid coupled in Step E with the appropriate amine, in this case cyclopropyl-(2-aminomethyl-4-chlorophenoxy)-acetamide (a method for the preparation of this class of amines is shown below) and the nitro group reduced in Step F by a reducing agent such as stannous chloride to give the final product.
- 10
- 15





Method for making ethyl-(2-aminomethyl-4-chlorophenoxy)-acetamide

- 4-Chlorosalicaldehyde is condensed with hydroxylamine hydrochloride in ethanolic aqueous sodium carbonate solution in Step A. The oxime is reduced by hydrogenation over a catalyst such as rhodium and the amine is protected as its BOC derivative under standard conditions. The phenol is alkylated in Step D with an acetate equivalent such as ethyl bromoacetate and the resulting ester is hydrolysed with lithium hydroxide. The product carboxylic acid is coupled to an amine such as ethylamine or cyclopropylamine in Step F, and the BOC group is removed by strong acid such as TFA in Step G.



Modifications of this method will allow different R⁴ and R⁵ groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. For example, appropriate choice of the amine in Step F will allow different values of R¹⁰ and R¹¹ to

be achieved. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

5 **Step A: 4-Chlorosalicaldehyde Oxime**

A solution of hydroxylamine hydrochloride (16.7 g, 0.24 mol) and sodium carbonate (12.7 g, 0.12 mol) in water (120 ml) was added to a stirred solution of 4-chlorosalicaldehyde (25.0 g, 0.16 mol) in ethanol (160 ml) and the resulting solution was heated to reflux. After 1 h the
10 reaction was cooled, water (320 ml) was added and the resulting crystalline precipitate was isolated by filtration. A second crop was similarly collected and the combined solids were dried to give the title compound:

15 ^1H NMR (CDCl_3) δ 6.92 (d, $J=8.8\text{Hz}$, 1 H), 7.15 (d, $J=2.6\text{Hz}$, 1H), 7.23 (dd, $J=2.6$ and 8.8 Hz , 1H), 7.26 (s, 1H), 8.16 (s, 1H), 9.71 (s, 1H).

Step B: 2-Hydroxy-5-Chlorobenzylamine

A mixture of 4-chlorosalicaldehyde oxime (10 g, 58.3 mmol) and 5% Rh/C (2.0 g) in ethanol (100 ml) containing concentrated sulfuric acid (10 ml) was shaken in a Parr apparatus under H_2 (60 psi) for 24 h.
20 Water (100 ml) was added and the mixture was filtered through celite. The filtrate was concentrated until the product had crystallized out of solution. The solid was collected by filtration and the filtrate was further concentrated, adding water to give a second crop which was combined
25 with the first to give after drying the title compound:

^1H NMR (CD_3OD) δ 4.07 (s, 2 H), 6.88 (d, $J=8.6\text{Hz}$, 1 H), 7.25 (dd, $J=2.6$ and 8.6Hz , 1H), 7.31 (d, $J=2.6\text{Hz}$, 1 H).

Step C: N-t-Butoxycarbonyl-2-Hydroxy-5-Chlorobenzylamine

A mixture of 2-hydroxy-5-chlorobenzylamine (1.22 g, 4.77 mmol assuming the bisulfate salt), (BOC)₂O (1.56 g, 7.16 mmol) and N-methylmorpholine (1.05 ml, 9.54 mmol) in DMF (10 ml) was stirred for 5 h at r.t. The reaction was partitioned between water and ethyl acetate and the organic layer was washed with 5% KHSO₄ solution (2 times), sodium hydrogen carbonate solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to a solid. The crude product was recrystallized from ethyl acetate/hexanes (1:5, 12 ml) to give the title compound:
10 ¹H NMR (CDCl₃) δ 1.44 (s, 9 H, t-Bu), 4.17 (d, J=6.8Hz, 2H, CH₂), 5.22 (br t, 1H, NH), 6.87 (d, J=8.6Hz, 1H, H-3), 7.03 (d, J = 2.6Hz, 1H, H-6), 7.15 (dd, J=2.6 and 8.6 Hz, 1H, H-4).

Step D: Ethyl-(2-t-Butoxycarbonylaminomethyl-4-Chlorophenoxy)-Acetate

A mixture of N-t-butoxycarbonyl-2-hydroxy-5-chlorobenzylamine (730 mg, 2.83 mmol), Cs₂CO₃ (923 mg, 2.83 mmol) and ethylbromoacetate (0.314 ml, 2.83 mmol) in DMF (5 ml) was stirred for 2 h. The crude reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with brine, dried (Na₂SO₄) and evaporated *in vacuo* to an oil which was used for the next step.

Step E: 2-t-Butoxycarbonylaminomethyl-4-Chlorophenoxyacetic Acid

The product from Step D was suspended in 1:1:1 methanol/THF/ water (9 ml) and lithium hydroxide hydrate (126 mg, 3.0 mmol) was added. After 16 h the volatiles were removed *in vacuo* and the solution was diluted with water and was washed with ethyl acetate, adding sufficient brine to disperse the emulsion. The aqueous layer was acidified with 5% KHSO₄ solution and was extracted with methylene chloride which was then dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a solid:
30 ¹H NMR (CDCl₃) δ 1.44 (s, 9H, t-Bu), 4.35 (br s, 2H, NCH₂), 4.62 (s, 2H, OCH₂), 5.04 (br s, 1H, NH), 6.74 (d, J=7.9Hz, 1H, H-3), 7.20 (d, J=2.6Hz, 1H, H-6), 7.24 (d obscured, 1H, H-4).

Step F: Ethyl-(2-t-Butoxycarbonylaminoethyl-4-Chlorophenoxy)-Acetamide

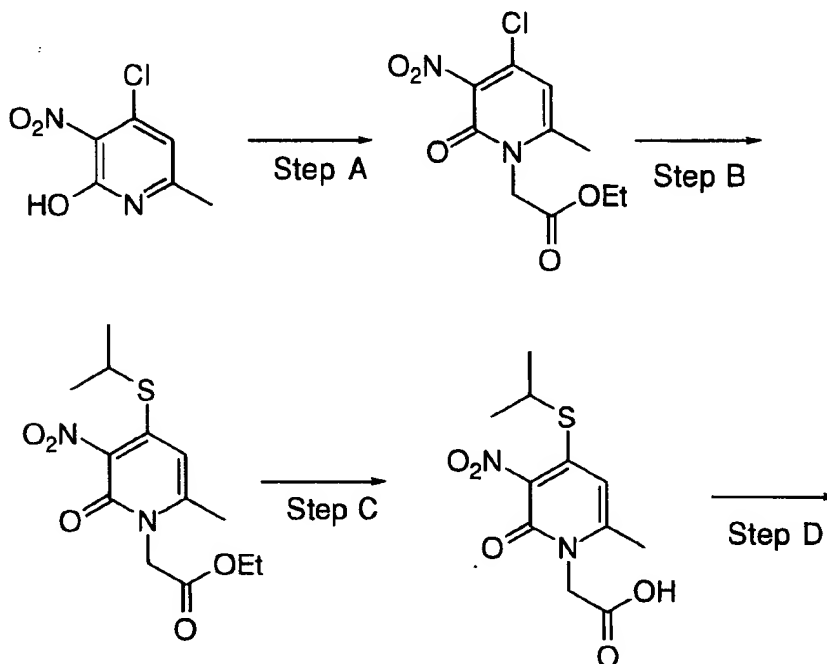
- EDC Hydrochloride (249 mg, 1.3 mmol) was added to a stirred mixture of 2-t-butoxycarbonylaminoethyl-4-chlorophenoxyacetic acid (316 mg, 1.0 mmol), HOBT (176 mg, 1.3 mmol), ethylamine hydrochloride (106 mg, 1.3 mmol) and N-methylmorpholine (0.396 ml, 3.6 mmol) in DMF (4 ml) and the mixture was stirred for 16 h. The reaction was partitioned between ethylacetate and 5% KHSO₄ solution and the organic layer was washed with 5% KHSO₄ solution, water, NaHCO₃ solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to a solid (333 mg) which was used for the next step.

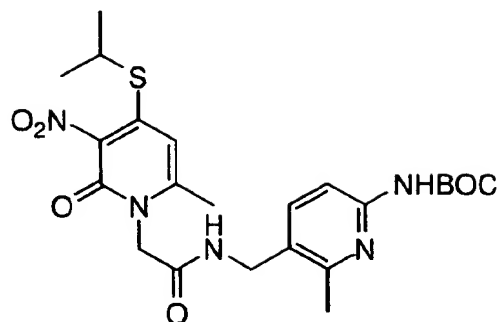
Step G: Ethyl-(2-Aminoethyl-4-Chlorophenoxy)-Acetamide

- Ethyl-(2-t-butoxycarbonylaminoethyl-4-chlorophenoxy)-acetamide from Step F was dissolved in 2:1 methylene chloride/TFA (3 ml) and after 15 min the solvent was evaporated *in vacuo*. The residue was dissolved in water and the solution was washed with methylene chloride (twice). The aqueous layer was then basified with saturated sodium carbonate solution and NaCl was added to saturation. The mixture was extracted with ethyl acetate, and the organic layer was dried (Na₂SO₄) and evaporated *in vacuo* to give the title compound as a crystalline solid:
- ¹H NMR (300 MHz, CDCl₃) δ 1.12 (t, J=7.3 Hz, 3H, Me), 1.54 (s, 9H, t-Bu), 3.31 (quintet, J=7.3 Hz, 2H, CH₂Me), 3.90 (s, 2H, NCH₂), 4.58 (s, 2H, OCH₂), 6.80 (d, J=8.3 Hz, 1H, H-3), 7.19-7.23 (m, 2H, H-4, H-6), 8.01 (br s, 1H, CONH).

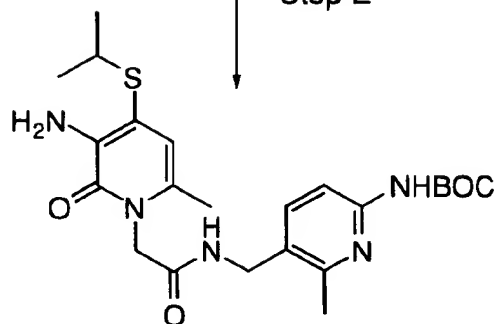
METHOD 2 (AS EXEMPLIFIED BY EXAMPLE III)

The product of METHOD 1, Step A is alkylated with an acetate equivalent such as ethyl bromoacetate in Step A which is then
5 reacted with the thiol in Step B. The ester is then hydrolysed in Step C with lithium hydroxide and the resulting carboxylic acid is coupled with the appropriate amine, in this case 5-aminomethyl-2-t-butoxycarbonylamino-6-methylpyridine (a method for the preparation of this amine is shown below) in Step D. The nitro group is reduced in Step
10 E with hydrogen in the presence of a catalyst such as palladium on carbon and the BOC group removed by a strong acid such as HCl in Step F to give the final product.

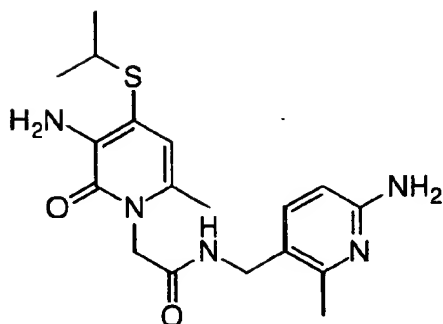




Step E



Step F



Modifications of METHODS 1 and 2 will allow different W,
R², R³ and A groups contemplated by the scope of the broad claim below
5 to be present by the use of an appropriate reagent or appropriately

substituted starting material in the indicated synthetic step. For example the starting pyridine in Step A can have as its side chain at the 6-position, ethyl, isopropyl, cyclopropyl, trifluoromethyl, and the like, to achieve the different operable values of R^3 . Similarly the thiol in Step B can have as its R^2 group, benzyl, cyclopropylmethyl, and the like, to achieve the different operable values of R^2 . An appropriate choice of the amine in the coupling step will allow the different operable values of A to be achieved. Different W groups may be introduced by such methods as alkylation, acylation or sulfonylation of the products of METHOD 1, Step F and METHOD 2, Step E. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

15 Method for making 5-aminomethyl-2-t-butoxycarbonylamino-6-methylpyridine

Preparation of 2-Amino-5-cyano-6-methylpyridine

 A mixture of 2-amino-5-bromo-6-methylpyridine (20.0 g, 0.107 mol) (Maybridge) and copper (I) cyanide 11.0 g, 0.123 mol) in DMF (25 ml) was heated to reflux for 4 h. The DMF was evaporated *in vacuo* and the residue was partitioned between ethyl acetate and 10% sodium cyanide solution. The organic layer was washed with 10% sodium cyanide solution and brine, dried (Na_2SO_4) and evaporated *in vacuo* to a brown solid. This was dissolved in a minimum amount of ethyl acetate and the product was precipitated by adding hexanes. The mixture was filtered to give the title compound as a brown powder:
 ^1H NMR (CDCl_3) δ 2.56 (s, 3 H), 4.97 (br s, 2 H), 6.33 (d, $J = 8.6$ Hz, 1 H), 7.54 (d, $J = 8.6$ Hz, 1 H).

30 Preparation of 2-t-Butoxycarbonylamino-5-cyano-6-methylpyridine

 A mixture of 2-amino-5-cyano-6-methylpyridine (10.0 g, 75.1 mmol), $(\text{BOC})_2\text{O}$ (16.39 g, 75.1 mmol), triethylamine (11.5 ml, 82.6 mmol) and DMAP (0.92 g, 7.5 mmol) in methylene chloride (200 ml) was stirred for 3 h. More triethylamine (4.22 ml) and $(\text{BOC}_2)\text{O}$ (1.64 g) were added and after 16 h the reaction was diluted with ethyl acetate and was

washed with 1 M AcOH (3 times), dried (Na₂SO₄) and evaporated *in vacuo* to give dark brown solid. The crude product was purified by flash column chromatography (10% ethylacetate/hexanes) to give the title compound as a white solid:

- 5 ¹H NMR (CDCl₃) δ 1.52 (s, 9 H), 2.62 (s, 3 H), 7.46 (br s, 1 H), 7.80 (d, J = 8.8 Hz, 1 H), 7.88 (d, J = 8.8 Hz, 1 H).

Preparation of 5-aminomethyl-2-t-butoxycarbonylamino-6-methylpyridine

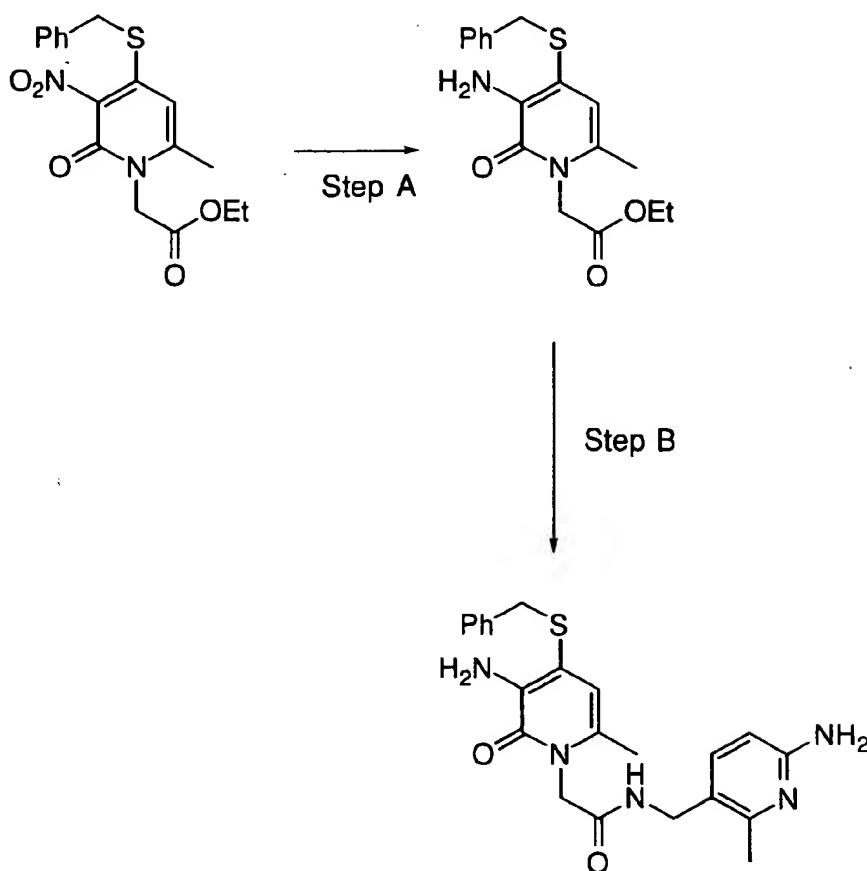
- 10 A mixture of 2-t-butoxycarbonylamino-5-cyano-6-methylpyridine (14.68 g, 62.9 mmol) and 10% Pd/C (1.5 g) in glacial acetic acid (150 ml) was shaken on a Parr apparatus at 60 psi for 88 h. The reaction was filtered through celite and was evaporated *in vacuo*. The residue was dissolved in water and the solution was washed with
15 methylene chloride (2 times), then was basified with sodium carbonate and extracted with ethyl acetate (2 times). The combined ethyl acetate layers were dried (Na₂SO₄) and evaporated *in vacuo* to a solid. The crude product was recrystallized (ethyl acetate/hexanes) to give the title compound:
20 ¹H NMR (CDCl₃) δ 1.50 (s, 9 H), 2.43 (s, 3 H), 3.81 (s, 2 H), 7.23 (br s, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 7.70 (d, J = 8.3 Hz, 1 H).

- Modifications of this method will allow different R¹² and R¹³ groups contemplated by the scope of the broad claim below to be present by
25 the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

30 **METHOD 3 (as exemplified by Example X)**

- The product of METHOD 2, Step B, in this case where R² is benzyl, is reduced in Step A with a reducing agent such as iron in acetic acid to give the amine. The ester is then hydrolysed and coupled with
35 the appropriate amine, in this case 2-amino-5-aminomethyl-6-

methylpyridine (a method for the preparation of this amine is shown below) in Step B to give the final product.



5

Modifications of this Method will allow different W, R², R³ and A groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. For example the starting pyridinone in Step A can have as its side chain at the 6-position, ethyl, isopropyl, cyclopropyl, trifluoromethyl, and the like, to achieve the different operable values of R³. Similarly it can have as its R² group, phenyl, cyclopropylmethyl, and the like, to achieve the different operable values of R². An appropriate choice of the amine in Step C will allow the different operable values of A to be achieved. Different W groups may be

15

introduced by such methods as alkylation, acylation or sulfonylation of the product of Step A. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

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Preparation of 2-Amino-5-methylamino-6-methylpyridine
dihydrochloride

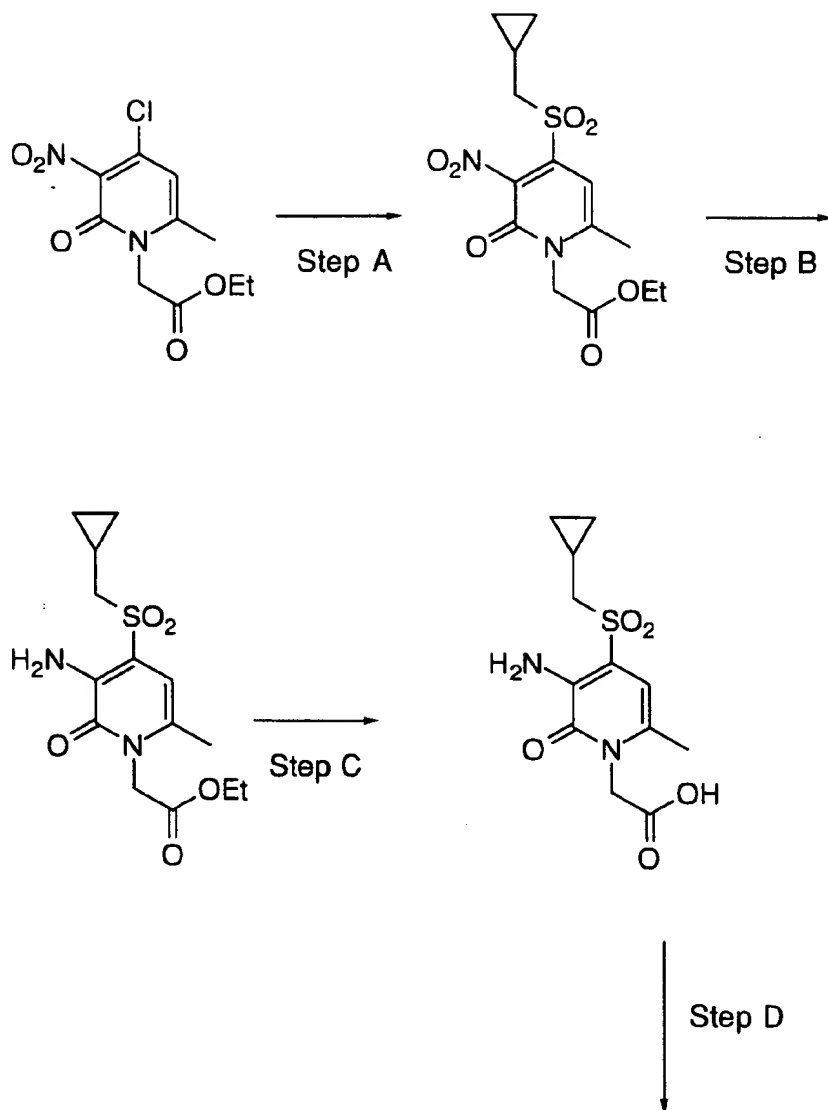
A mixture of 2-amino-5-cyano-6-methylpyridine (4.0 g, 30.0 mmol) and 10% Pd/C (3.08 g) in ethanol (80 mL), methanol (30 mL),
10 concentrated HCl (6 mL) and water (10 mL) was shaken on a Parr apparatus at 60 psi for 25 h. The reaction was filtered through celite, rinsing with 1:1 ethanol/methanol and was evaporated *in vacuo* to a solid, which was triturated with 5:1 ethyl acetate/ethanol to give the title compound (5.95 g, 94%):
15 ¹H NMR (CD₃OD): δ 2.58 (s, 3 H), 4.12 (s, 2 H), 6.92 (d, J = 9.2 Hz, 1 H), 7.93 (d, J = 9.2 Hz, 1 H).

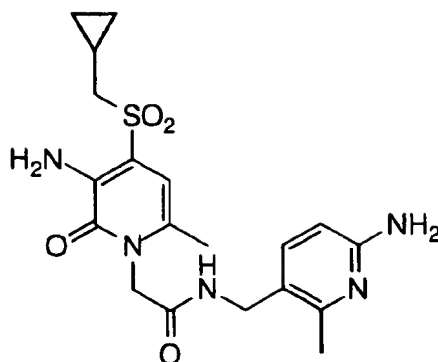
Modifications of this method will allow different R¹² and R¹³ groups contemplated by the scope of the broad claim below to be
20 present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

25

METHOD 4 (as exemplified by Example IV)

The product of METHOD 2, Step A is reacted with a sulfinate salt in this case where R² is cyclopropylmethyl in a solvent such as ethanol or DMF in Step A to give the sulfone. The nitro group may be reduced in Step B with hydrogen in the presence of a catalyst such as
30 palladium on carbon, the ester hydrolysed in Step C and the resulting carboxylic acid coupled to with the appropriate amine, in this case 2-amino-5-aminomethyl-6-methylpyridine, in Step D to give the final product.

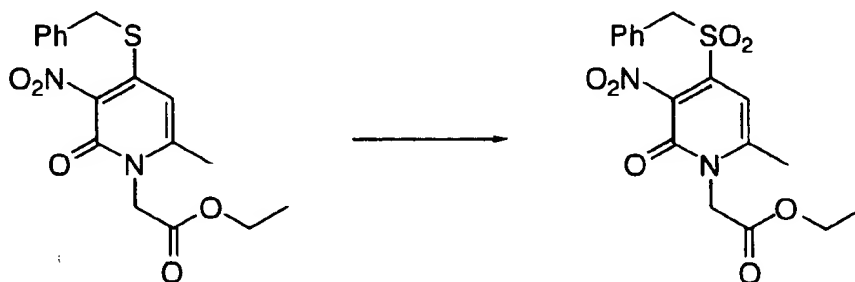




- Sulfinate salts used in the preparation of compound of the invention may be generated from the sulfinic acids. They may also be generated by a number of other methods, including the reductive cleavage of 2-sulfonylbenzothiazoles, the reaction of organometallics with sulfur dioxide, the reduction of sulfonyl chlorides, the oxidation of thiols and the cleavage of phthalimidomethyl sulfones.
- Modifications of this method will allow different W, R², R³ and A groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately substituted starting material in the indicated synthetic step. For example the starting pyridinone in Step A can have as its side chain at the 6-position, ethyl, isopropyl, cyclopropyl, trifluoromethyl, and the like, to achieve the different operable values of R³. Similarly the sulfinate in Step A can have as its R² group, benzyl, cyclopentyl, and the like, to achieve the different operable values of R². An appropriate choice of the amine in Step D will allow the different operable values of A to be achieved.
- Different W groups may be introduced by such methods as alkylation, acylation or sulfonylation of the product of Step B. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

METHOD 5 (as exemplified by Example VIIb)

The product of METHOD 2, Step B, in this case where R² is benzyl, may be oxidized with a suitable oxidizing agent such as
5 OXONE® or a peracid such as mCPBA to give the sulfone which may be further manipulated, for example by the procedures of METHOD 4, Steps B-D, to give the products of the invention.



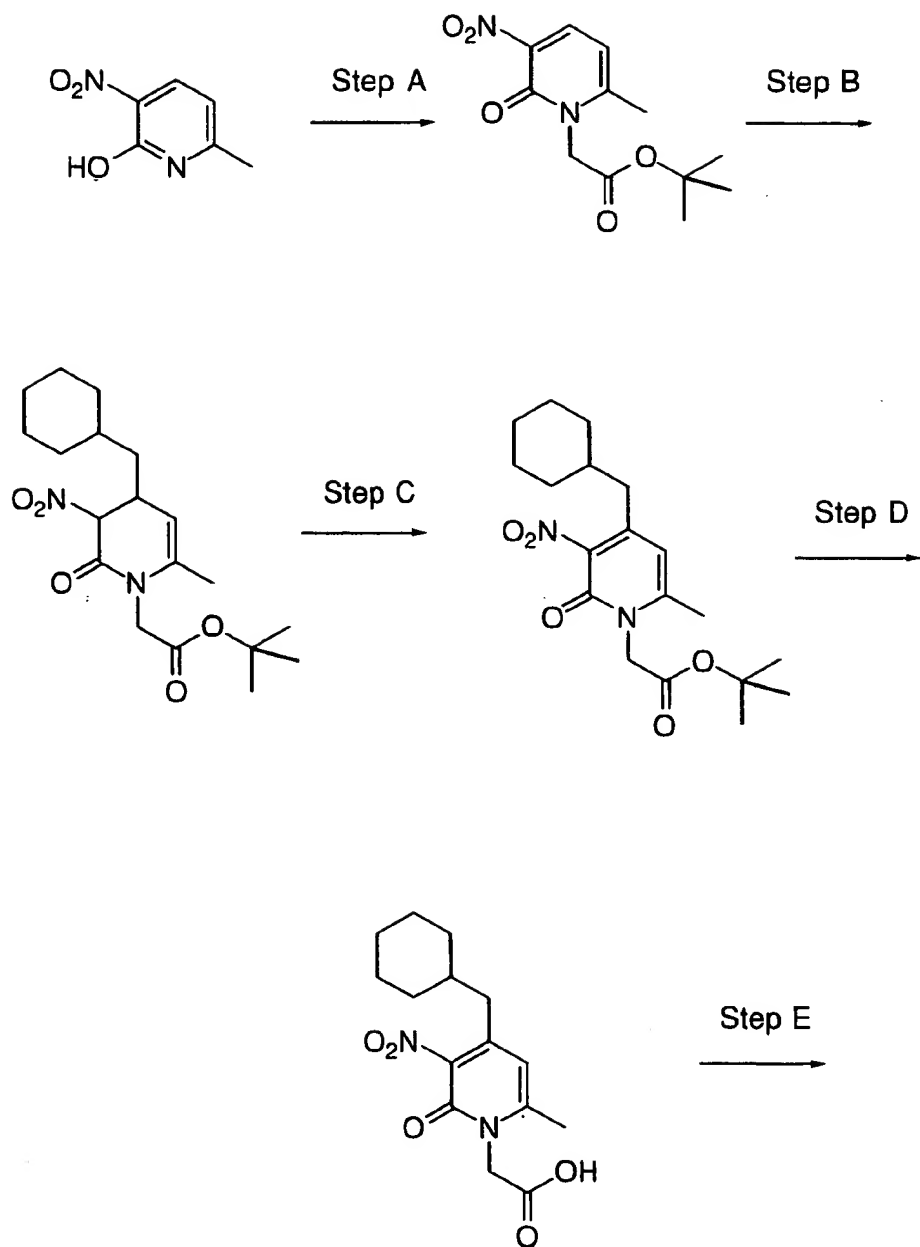
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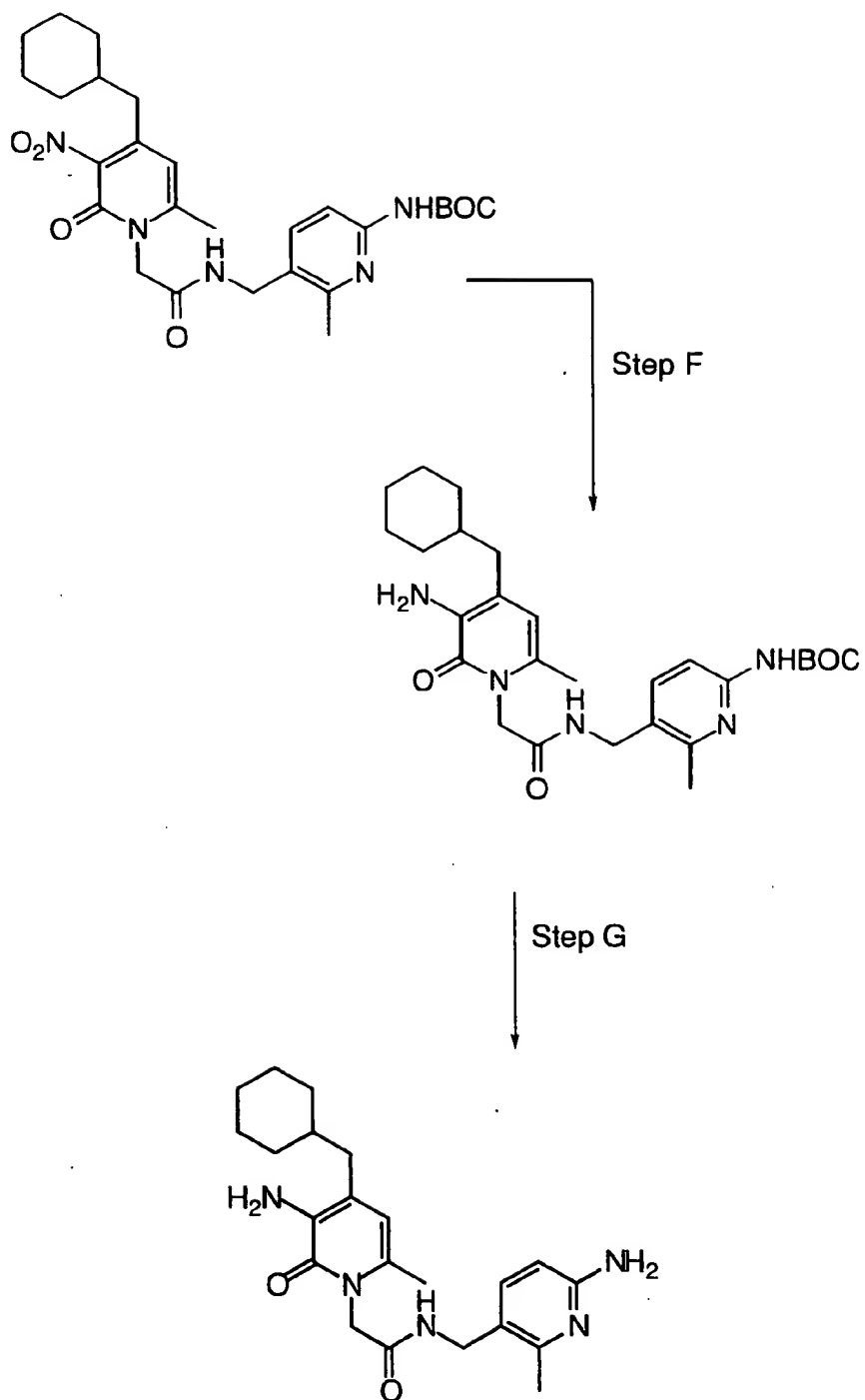
The compounds of the present invention, where X is CR¹⁵R¹⁶, may be prepared using METHODS 6 and 7:

METHOD 6 (as exemplified by Example XI)

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The starting 2-hydroxy-3-nitropyridine is alkylated with an acetate equivalent such as t-butyl bromoacetate in Step A to give the pyridinone. This is reacted with an organomagnesium reagent, in this case cyclohexylmethyl magnesium bromide, in Step B. The resulting
20 lactam is oxidised in Step C with an oxidising agent such as DDQ or nickel peroxide to regenerate the pyridinone. The t-butyl group is removed using a strong acid such as HCl in Step D and the resulting carboxylic acid coupled with the appropriate amine, in this case 2-BOC-amino-5-aminomethyl-6-methylpyridine in Step E. The nitro group is
25 reduced in Step F by hydrogenation using a catalyst such as palladium on carbon and the the BOC group is removed in Step G with a strong acid such as TFA to give the final product.

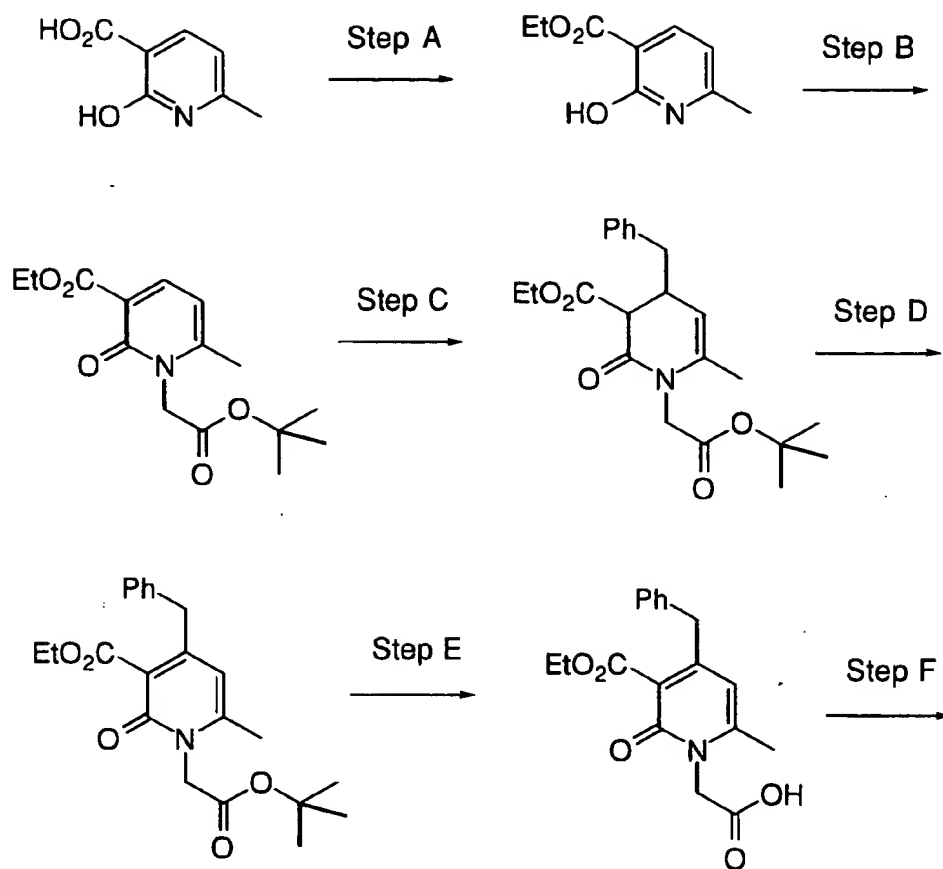


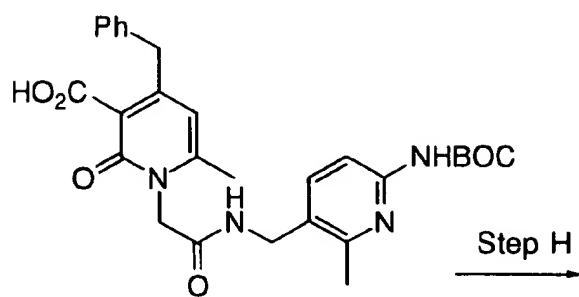
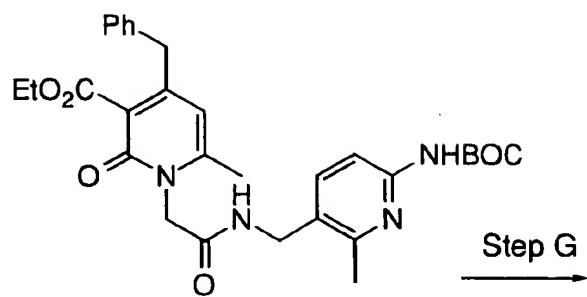


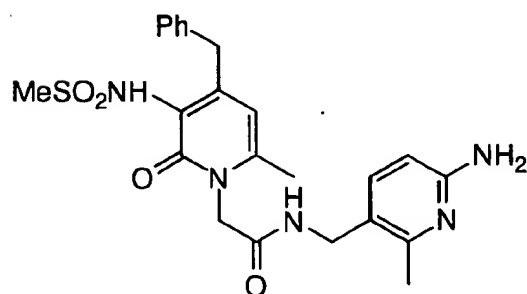
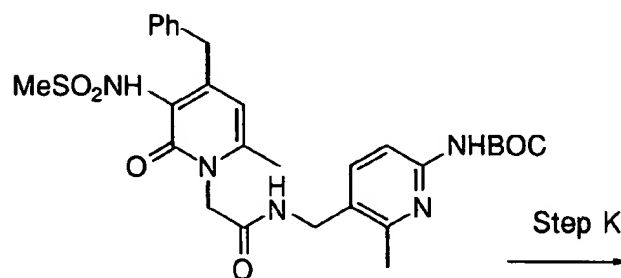
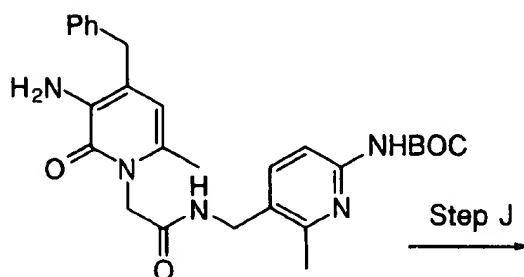
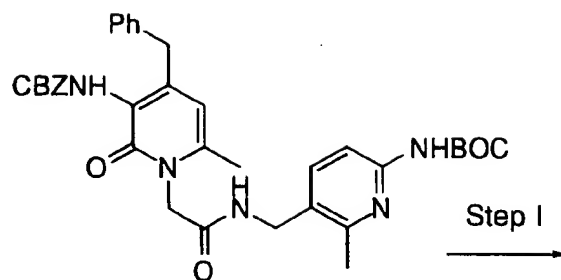
METHOD 7 (as exemplified by Example I)

The starting acid is esterified in Step A and is alkylated with t-butyl bromoacetate in Step B. The resulting pyridinone is reacted with an organomagnesium reagent, in this case benzyl magnesium chloride, in Step C and the lactam is oxidised in Step D with an oxidising agent such as DDQ or nickel peroxide to regenerate the pyridinone. The t-butyl group is removed using a strong acid such as TFA in Step E and the resulting carboxylic acid coupled with the appropriate amine, in this case 2-BOC-amino-5-aminomethyl-6-methylpyridine in Step F. The ethyl ester is hydrolysed with lithium hydroxide in Step G and the acid was rearranged to the isocyanate via the acyl azide using DPPA and a base such as triethylamine followed by heating in Step H. The intermediate isocyanate is then reacted with benzyl alcohol in the presence of a base to give the CBZ derivative. The CBZ group was removed by hydrogenolysis in Step I using a catalyst such as palladium and the amine is then sulfonylated in Step J, in this case with methane sulfonyl chloride, in the presence of a base such as pyridine. The BOC group is removed in Step K with a strong acid such as TFA to give the final product.

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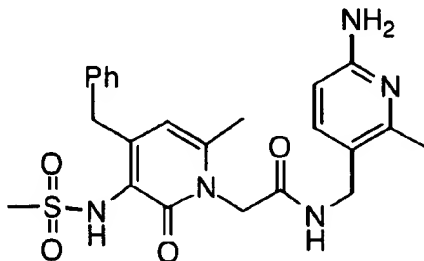


- 5 Modifications of METHODS 6 and 7 will allow different W, R², R³ and A groups contemplated by the scope of the broad claim below to be present by the use of an appropriate reagent or appropriately

substituted starting material in the indicated synthetic step. For example the starting pyridine can have as its side chain at the 6-position, ethyl, isopropyl, cyclopropyl, trifluoromethyl, and the like, to achieve the different operable values of R^3 . Different operable values of R^2 may be achieved by the appropriate choice of the organometallic reagent. An appropriate choice of the amine in the coupling step will allow the different operable values of A to be achieved. Different W groups may be introduced by such methods as alkylation, acylation or sulfonylation of the products from METHOD 6, Step F, and METHOD 7, Step I. Obvious variations and modifications of the method to produce similar and obvious variants thereof, will be apparent to one skilled in the art.

Amide couplings to form the compounds of this invention can be performed by the carbodiimide method with reagents such as dicyclohexylcarbodiimide, or 1-ethyl-3-(3-dimethyl-aminopropyl) carbodiimide. Other methods of forming the amide or peptide bond include, but are not limited to the synthetic routes via an acid chloride, azide, mixed anhydride or activated ester. Typically, solution phase amide couplings are performed, but solid-phase synthesis by classical Merrifield techniques may be employed instead. The addition and removal of one or more protecting groups is also typical practice.

The following examples are illustrative of the invention as contemplated by the inventors and should not be construed as being limits on the scope or spirit of the instant invention.

EXAMPLE IPreparation of 3-Methanesulfonylamino-4-benzyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinoneI-11

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Step A: Ethyl 6-methylpyridin[1H]-2-one-3-carboxylate (I-1)

To a stirred slurry of 7.66 g (50 mmol) of 2-hydroxy-6-methylpyridine-3-carboxylic acid, 3.52 mL (60 mmol) of anhydrous ethanol, and 611 mg (5 mmol) of 4-(N,N-dimethylamino)pyridine (DMAP) in 100 mL of CH₂Cl₂ was added 10.32 g (50 mmol) of dicyclohexylcarbodiimide (DCC) and the mixture stirred overnight at ambient temperature. The mixture was filtered and the precipitate was washed with minimal CH₂Cl₂. The filtrate was concentrated and crystallized from 100 mL of ethyl acetate to give I-1 as a colorless solid: ¹H NMR (CDCl₃) δ 8.15 (d, 1H, 7.5 Hz), 6.3 (br s, 1H), 4.37 (q, 2H, 7.1 Hz), 2.46 (s, 3H), 1.38 (t, 3H, 7.1 Hz).

Step B: Ethyl 6-methyl-1-(t-butyl acetate)pyridin[1H]-2-one-3-carboxylate (I-2)

To a 0°C stirred suspension of 3.5 g (19.3 mmol) of ethyl 6-methylpyridin-2-one-3-carboxylate in 50 mL anhydrous THF under Ar was added 0.8 g (20 mmol) of NaH (60% in oil) in portions over a 2 min period. After the mixture became homogeneous over 10 min, 3.55 mL (22 mmol) of t-butyl bromoacetate was added dropwise. The cold bath was removed and the reaction mixture stirred under Ar overnight.

Concentration of the reaction mixture at reduced pressure gave a residue that was partitioned between CHCl_3 and 1M citric acid. The aq. layer was extracted with CHCl_3 , and the combined organic layers washed with 10% Na_2CO_3 , dried over Na_2SO_4 and the solvents removed to give an oil that was chromatographed on 75 g of SiO_2 using 98.5:1.5 to 95:5 CHCl_3 - CH_3OH which gave **I-2** as a colorless solid: ^1H NMR (CDCl_3) δ 8.1 (d, 1, 7.3 Hz), 6.13 (d, 1H, 7.3 Hz), 4.78 (s, 2H), 4.35 (q, 2H, 7.1 Hz), 2.34 (s, 3H), 1.48 (s, 9H), 1.37 (t, 3H, 7.1 Hz).

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Step C: Ethyl 4-benzyl-3,4-dihydro-6-methyl-1-(t-butyl acetate)pyridin[1H]-2-one-3-carboxylate (**I-3**)

To a stirred -78° solution of 1.0 g (3.39 mmol) of ethyl 6-methyl-1-(t-butyl acetate)pyridin-2-one-3-carboxylate in 20 mL of anhydrous THF was added a 2M THF solution of benzylmagnesium chloride dropwise. After stirring for 15 min at -78 , the reaction was stored in the freezer (approx. -15°C) overnight. After quenching with 200 μL (3.5 mmol) of acetic acid, the reaction was concentrated at reduced pressure, diluted with cold 5% HCl and extracted with EtOAc. The organic layer was washed with sat. NaHCO_3 , brine, dried over Na_2SO_4 and concentrated at reduced pressure to give an oil that was chromatographed on 50 g SiO_2 using 11:29 EtOAc-hexane.

Concentration of the fractions at reduced pressure provided **I-3** as a colorless oil: ^1H NMR (CDCl_3) δ 7.35-7.15 (m, 5H), 4.94 (d, 1H, 4.4 Hz), 4.54 (d, 1H, 17.5 Hz), 4.3-4.1 (m, 2H), 4.08 (d, 1H, 17.6 Hz), 3.35 (d, 1H, 7.3 Hz), 3.15-3.05 (m, 1H), 2.8-2.65 (m, 2H), 1.83 (t, 3H, 1.3 Hz), 1.47 (s, 9H), 1.25 (t, 3H, 7.1 Hz).

Step D: Ethyl 4-benzyl-6-methyl-1-(t-butyl acetate)pyridin[1H]-2-one-3-carboxylate (**I-4**)

To a stirred solution of 690 mg (1.78 mmol) of ethyl 4-benzyl-3,4-dihydro-6-methyl-1-(t-butyl acetate)pyridin[1H]-2-one-3-carboxylate in 7 mL of dioxane was added 445 mg (1.95 mmol) of 2,5-dichloro-3,6-

dicxano-1,4-benzoquinone (DDQ). After heating at 70°C for 24 h under Ar, the cooled reaction mixture was diluted with 21 mL of benzene and the precipitate removed by filtration. Concentration at reduced pressure, followed by chromatography of the residue on 15 g SiO₂ using 1:2 to 2:3 EtOAc-hexane provided **I-4** as a pale yellow solid: ¹H NMR (CDCl₃) δ 7.35-7.2 (m, 5H), 5.81 (s, 1H), 4.69 (s, 2H), 4.34 (q, 2H, 7.1 Hz), 3.82 (s, 2H), 2.19 (s, 3H), 1.46 (s, 9H), 1.31 (t, 3H, 7.1 Hz).

Step E: Ethyl 4-benzyl-6-methyl-1-carboxymethylpyridin[1H]-2-one-3-carboxylate (**I-5**)

To a stirred solution of 456 mg (1.18 mmol) of ethyl 4-benzyl-6-methyl-1-(t-butyl acetate)pyridin[1H]-2-one-3-carboxylate in 30 mL of CH₂Cl₂ was added 15 mL of trifluoroacetic acid (TFA). After stirring for 4 h under Ar, the reaction mixture was concentrated, dissolved in 30 mL of DMF and re-concentrated to give **I-5**, a sticky yellow solid which was used directly in the following reaction.

Step F: 4-Benzyl-3-(ethoxycarbonyl)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (**I-6**)

To a stirred solution of 200 mg (0.61 mmol) of ethyl 4-benzyl-6-methyl-1-carboxymethylpyridin[1H]-2-one-3-carboxylate and 144 mg (0.61 mmol) of 2-t-butyloxycarbonylamino-5-aminomethyl-6-methylpyridine in 10 mL of CH₂Cl₂ was added 126 mg (0.61 mmol) of dicyclohexylcarbodiimide (DCC) under Ar. After stirring for 3 h, the precipitate that had formed was removed by filtration, washed with minimal CH₂Cl₂, and the filtrate was diluted and washed with 1M citric acid, 5% NaHCO₃, dried over Na₂SO₄ and concentrated at reduced pressure to give **I-6** as a pale yellow solid: ¹H NMR (CDCl₃) δ 7.64 (d, 1H, 8.4 Hz), 7.41 (d, 1H, 8.4 Hz), 7.35-7.2 (m, 5H), 7.09 (s, 1H), 5.90 (s, 1H), 4.65 (br s, 2H), 4.4-4.3 (m, 4H), 3.83 (s, 2H), 2.41 (s, 3H), 2.36 (s, 3H), 1.51 (s, 9H), 1.32 (t, 3H, 7.1 Hz).

Step G: 4-Benzyl-3-carboxy-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (I-7)

A 348 mg (0.63 mmol) sample of 4-benzyl-3-(ethoxycarbonyl)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one was dissolved in 10 mL of 1,2-dimethoxyethane and treated with 2.5 mL of 1M LiOH under Ar for 16 h at 40°C. The reaction mixture was concentrated at reduced pressure and partitioned between EtOAc and 1M citric acid. The organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated at reduced pressure to give I-7 as a yellow solid which was used directly in the following reaction.

Step H: 4-Benzyl-3-(benzyloxycarbonylamino)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (I-8)

A solution of 281 mg (0.54 mmol) of 4-benzyl-3-carboxy-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one, 117 µL (0.54 mmol) of diphenylphosphoryl azide, and 75 µL (0.54 mmol) of triethylamine (TEA) were heated to 50-60°C in 3 mL of dioxane under Ar for 20 h. Benzyl alcohol (61µL, 0.59 mmol) and a second portion of triethylamine were added and heating continued for 20 h. The reaction mixture was concentrated at reduced pressure and partitioned between CHCl₃ and 1M citric acid. The aqueous layer was extracted with CHCl₃ and the combined organic layers were washed with 10% Na₂CO₃, dried over Na₂SO₄ and the solvents removed to give an oil that was chromatographed on 20 g SiO₂ using 95:5 CHCl₃/CH₃OH to give I-8 as a green tinted oil: ¹H NMR (CDCl₃) δ 7.64 (d, 1H, 8.3 Hz), 7.42-7.2 (m, 10H), 6.68 (br s, 1H), 5.85 (s, 1H), 5.16 (s, 2H), 4.64 (s, 2H), 4.29 (d, 2H, 5.6 Hz), 3.88 (s, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 1.50 (s, 9H).

Step I: 4-Benzyl-3-amino-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (**I-9**)

A stirred solution of 185 mg (0.3 mmol) of 4-benzyl-3-(benzyloxycarbonylamino)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one in 11 mL of ethanol was hydrogenated with 41 mg of 20% Pd(OH)₂ on carbon using a balloon overnight. The catalyst was removed by filtration, washed with ethanol, and the filtrate concentrated at reduced pressure to give **I-9** as an oily residue which was carried forward to the next step.

Step J: 4-Benzyl-3-(methanesulfonylamino)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (**I-10**)

The product from Step I was dissolved in 3 mL of pyridine, cooled in an ice bath and treated with 28 μ L (0.36 mmol) of methanesulfonyl chloride dropwise. The cold bath was allowed to expire over a 2.5 h period, the reaction concentrated at reduced pressure, partitioned between CHCl₃ and 1M citric acid. The organic layer was washed with 5% NaHCO₃, dried over Na₂SO₄, treated with activated carbon and concentrated to give a yellow oil that was chromatographed on 14 g of SiO₂ using 99:1 to 97:3 CHCl₃-CH₃OH to afford **I-10** as a colorless solid: ¹H NMR (CDCl₃) δ 7.69 (d, 1H, 8.1 Hz), 7.58 (br s, 1H), 7.45 (d, 1H, 8.4 Hz), 7.35-7.23 (m, 3H), 7.17 (d, 2H, 6.8 Hz), 6.94 (br t, 1H), 6.56 (s, 1H), 5.91 (s, 1H), 4.64 (s, 2H), 4.37 (d, 2H, 5.5 Hz), 4.13 (s, 2H), 2.82 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H), 1.51 (s, 9H).

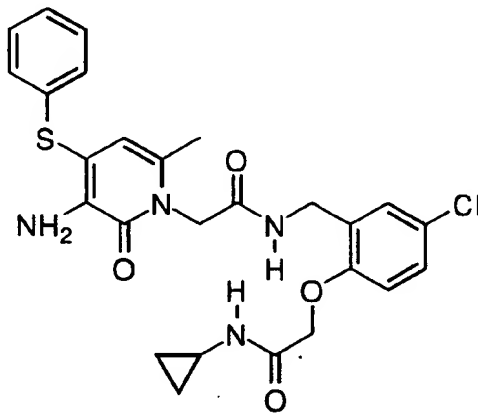
Step K: 4-Benzyl-3-methanesulfonylamino-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one (**I-11**)

To a stirred solution of 60 mg (0.1 mmol) of 4-benzyl-3-(methanesulfonylamino)-6-methyl-1-(2-t-butyloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl) pyridin[1H]-2-one in 8

mL of CH₂Cl₂ was added 4 mL of TFA under Ar. After stirring for 45 min, the reaction was concentrated at reduced pressure and retreated with TFA as above for an additional 30 min. The reaction was concentrated at reduced pressure and purified by gradient elution preparative HPLC using a C-18 stationary phase and 0.1% aqueous TFA/CH₃CN as the mobile phase. The fractions were assayed by analytical HPLC, combined and concentrated at reduced pressure to give a residue that was triturated with 1:4 EtOAc-hexane to provide I-11 as a colorless solid: ¹H NMR (D₆-DMSO) δ 13.55 (br s, 1H), 8.75 (br s, 2H), 7.74 (d, 1H, 7 Hz), 7.55 (br s, 2H), 7.4-7.15 (m, 5H), 6.76 (d, 1H, 7 Hz), 5.90 (s, 1H), 4.63 (s, 2H), 4.15 (br d, 2H), 3.95 (s, 2H), 2.98 (s, 3H), 2.40 (s, 3H), 2.18 (s, 3H).

EXAMPLE II

3-Amino-4-Phenylthio-6-Methyl-1-[Cyclopropyl-(2-Methylene-carboxamidomethyl-4-Chlorophenoxy)-Acetamidol-2-Pyridinone



II-6

Step A: 4-Chloro-2-hydroxy-6-methyl-3-nitropyridine (II-1)
POCl₃ (7.6 mL, 81.4 mmol) was added to a solution of 2,4-dihydroxy-6-methyl-3-nitropyridine (Fluka, 3.15 g, 18.5 mmol) and

BnEt₃NCl (16.8 g, 74 mmol) in MeCN (65 mL). The resulting solution was stirred at 40° C for 30 min then was heated at reflux for 1 h. After evaporation of the solvent, water (70 mL) was added and the mixture was stirred at room temperature for 16 h. The precipitate which formed was
5 filtered and washed with hexane to afford II-1 as a yellow solid.
1H NMR (DMSO-d₆) δ 2.25 (s, 3H), 6.45 (s, 1H).

Step B: 2-Hydroxy-6-Methyl-3-Nitro-4-Thiophenylpyridine (II-2)

To a solution of 4-chloro-2-hydroxy-6-methyl-3-nitropyridine
10 (188 mg, 1.0 mmol) in 2 mL of EtOH and 0.2 mL (1.4 mmol) of Et₃N was added 0.11 mL (1.0 mmol) of PhSH. Precipitation occurred immediately and the solution was allowed to stir at room temperature for 16 h. The solid was filtered and washed with EtOH to afford II-2.

15 Step C: 1-(t-Butyl-Methylenecarboxy)-6-Methyl-3-Nitro-4-Thiophenyl-2-Pyridinone (II-3)

To a 0° C solution of 2-hydroxy-6-methyl-3-nitro-4-thiophenylpyridine (171 mg, 0.654 mmol) in 2 mL of DMF was added 17 mg (0.72 mmol) of NaH. The solution was stirred at 0° C for 10 min
20 before the addition of 0.106 mL (0.72 mmol) of tert-butyl bromoacetate. After 3 h, the solvent was removed in vacuo and the residue was redissolved in 25 mL of EtOAc and washed with water (3x5 mL). The organic phase was dried (MgSO₄), concentrated and chromatographed (2/3 EtOAc / Hexane) to afford II-3.
25 1H NMR (CDCl₃) δ 7.50 (m, 5H), 5.45 (s, 1H), 4.65 (s, 2H), 2.15 (s, 3H), 1.46 (s, 9H).

Step D: 1-Methylenecarboxy-6-Methyl-3-Nitro-4-Thiophenyl-2-Pyridinone (II-4)

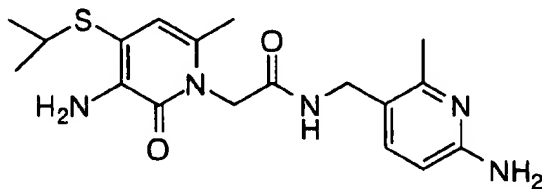
To a 0° C solution of 1-(t-butyl-methylenecarboxy)-6-methyl-3-nitro-4-thiophenyl-2-pyridinone (77 mg, 0.20 mmol) in 4 mL of DCM was added 1 mL of TFA. The solution was stirred at 0° C for 3 h, before the solvent was removed in vacuo and the residue was azeotroped with benzene, then EtOAc, then ether to afford II-4.
35 1H NMR (CDCl₃) δ 7.50 (m, 5H), 5.45 (s, 1H), 4.75 (s, 2H), 2.10 (s, 3H).

Step E: 6-Methyl-3-Nitro-4-Thiophenyl-1-[Cyclopropyl-(2-Methylenecarboxamidomethyl-4-Chlorophenoxy)-
Acetamidol-2-Pyridinone (II-5)

To a solution of 1-methylenecarboxy-6-methyl-3-nitro-4-thiophenyl-2-pyridinone (65.2 mg, 0.204 mmol) and N-cyclopropyl(2-aminomethyl-5-chlorophenoxy)acetamide (59 mg, 0.204 mmol) in 2 mL of DMF was added 39.0 mg (0.204 mmol) of EDCI and 28 mg (0.204 mmol) of HOBT followed by 0.177 mL (1.02 mmol) of DIPEA. The homogeneous mixture was stirred at room temperature for 16h after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with sat'd NaHCO₃ then water. The organic phase was dried (MgSO₄) and concentrated to afford II-5.
1H NMR (CDCl₃) δ 8.85 (bt, 1H), 8.00 (bs, 1H), 7.60 (m, 5H), 7.20 (m, 2H), 6.90 (d, J=8.8 Hz, 1H), 5.45 (s, 1H), 4.74 (s, 2H), 4.45 (s, 2H), 4.30 (d, J=4 Hz, 2H), 2.68 (m, 1H), 2.15 (s, 3H), 0.60 (m, 2H), 0.40 (m, 2H).

Step F: 3-Amino-6-Methyl-4-Thiophenyl-1-[Cyclopropyl-(2-Methylenecarboxamidomethyl-4-Chlorophenoxy)-
Acetamidol-2-Pyridinone (II-6)

To a solution of 6-methyl-3-nitro-4-thiophenyl-1-[cyclopropyl-(2-methylenecarboxamidomethyl-4-chlorophenoxy)-acetamido]-2-pyridinone (55.2 mg, 0.093 mmol) in 5 mL of EtOAc was added 107 mg (0.475 mmol) of SnCl₂·H₂O. The mixture was stirred at reflux for 16h, cooled and made basic by the addition of saturated NaHCO₃. The mixture was extracted with saturated NaHCO₃ then water. The organic phase was dried (MgSO₄) and concentrated to afford II-6 as a white solid.
1H NMR (CDCl₃) δ 7.65 (bs, 1H), 7.60 (m, 7H), 7.10 (bt, 1H), 6.75 (d, J=8.8 Hz, 1H), 6.00 (s, 1H), 4.68 (s, 2H), 4.55 (s, 1H), 4.40 (m, 3H), 3.50 (d, J=3 Hz, 1H), 2.88 (m, 1H), 2.30 (s, 3H), 0.70 (m, 4H).

EXAMPLE IIIPreparation of 3-Amino-4-isopropylthio-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinoneIII-6

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Step A: 4-Chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (III-1)

Sodium hydride (0.90 g of a 60% dispersion in mineral oil, 22.6 mmol) was added to a stirred solution of 4-chloro-2-hydroxy-6-methyl-3-nitropyridine (4.74 g, 25.1 mmol) in dry DMF (35 mL) at 0° C under nitrogen. After 20 min ethyl bromoacetate (3.35 mL, 30.2 mmol) was added and the mixture was warmed to room temperature. After 16 h, the solvent was evaporated in vacuo and the residue was partitioned between ethyl acetate and 10% citric acid solution. The organic layer was washed with water and brine, dried (Na₂SO₄) and evaporated to a heavy oil which was purified by flash column chromatography on silica (60% ethyl acetate/hexanes) to give III-1 as an orange solid.

¹H NMR (DMSO-d₆) δ 1.22 (t, J = 7.1 Hz, 3H), 2.41 (s, 3H), 4.18 (q, J = 7.1 Hz, 2H), 4.90 (s, 2H), 6.76 (s, 1H).

20

Step B: 4-Isopropylthio-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (III-2)

To a solution of 4-chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (500 mg, 1.82 mmol) in 10 mL of EtOH was added 0.22 mL (2.36 mmol) of isopropylthiol followed by 0.37 mL (2.7 mmol) of Et₃N. The solution was stirred at 82° C for 15 h, cooled and evaporated to an oil. The residue was partitioned between EtOAc and water and the organic phase was washed with brine, dried (MgSO₄) and

25

concentrated. Column chromatography (3:7 EtOAc / Hexanes) provided III-2 as a white solid.

¹H NMR (CDCl₃) δ 6.13 (s, 1H), 4.79 (s, 2H), 4.25 (q, J=7.4 Hz, 2H), 3.53 (m, 1H), 2.36 (s, 3H), 1.40 (d, J=6.8 Hz, 6H), 1.25 (t, J=7.4 Hz, 3H).

5

Step C: 4-Isopropylthio-6-methyl-3-nitro-1-methylenecarboxy-2-pyridinone (III-3)

A solution of 4-isopropylthio-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (330 mg, 1.04 mmol) in 5 mL of dioxane and 2 mL of water was treated with 132 mg (3.14 mmol) of LiOH.H₂O and the whole was stirred for 15h. The solvent was removed and the residue was treated with 4 mL of 1N HCl then washed with EtOAc (3 x 10 mL). The combined organic washings were dried over MgSO₄ and evaporated to leave III-3.

¹H NMR (CD₃OD) δ 6.54 (s, 1H), 4.84 (s, 2H), 3.78 (q, J=7.4 Hz, 1H), 2.40 (s, 3H), 1.35 (t, J=7.4 Hz, 3H).

Step D: 4-Isopropylthio-6-methyl-3-nitro-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (III-4)

To a solution of 4-isopropylthio-6-methyl-3-nitro-1-methylenecarboxy-2-pyridinone (150 mg, 0.523 mmol) and 2-amino-5-aminomethyl-6-methylpyridine (186 mg, 0.784 mmol) in 2 mL of DMF was added 200 mg (1.04 mmol) of EDCI and 141 mg (1.04 mmol) of HOBT followed by 0.36 mL (2.09 mmol) of DIPEA. The homogeneous mixture was stirred at room temperature for 16h after which time the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with sat'd NaHCO₃ then water. The organic phase was dried (MgSO₄) and concentrated to afford III-4 as a white solid.

¹H NMR (CDCl₃) δ 7.85 (bt, 1H), 7.44 (d, J=8 Hz, 1H), 7.30 (d, J=8Hz, 1H), 6.14 (s, 1H), 4.64 (bs, 2H), 4.25 (bs, 2H), 3.68 (q, J=7.4 Hz, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 1.50 (s, 9H), 1.35 (t, J=7.4 Hz, 3H).

35

Step E: 3-Amino-4-isopropylthio-6-methyl-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (III-5)

5 A solution of 4-isopropylthio-6-methyl-3-nitro-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone in 10 mL of THF was treated with 62 mg of 10% Pd on carbon and the whole was stirred under an atmosphere of H₂ for 16 h. The reaction mixture was filtered
10 through Celite and concentrated to afford III-5 as a tan colored foam which was used without further purification.
1H NMR (CDCl₃) δ 7.44 (d, J=8 Hz, 1H), 7.55 (s, 1H), 7.50 (bs, 1H), 7.40 (d, J=8Hz, 1H), 6.11 (s, 1H), 4.70 (bs, 1H), 4.54 (bs, 2H), 4.29 (bs, 2H), 3.39 (m, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 1.50 (s, 9H), 1.35 (d, J=7.4 Hz, 6H).

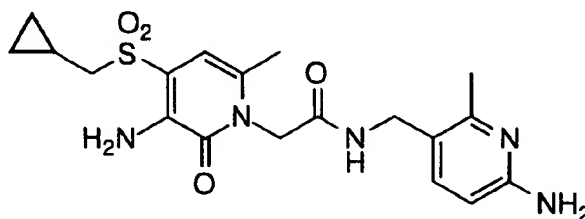
15 **Step F:** 3-Amino-4-isopropylthio-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (III-6)

A solution of 3-Amino-4-isopropylthio-6-methyl-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (140 mg, 0.294 mmol) in 10 mL of EtOAc and 5 mL of MeOH was treated with HCl gas for 2 minutes. The flask was capped and the reaction mixture was allowed to stir for 1h. The solvent was removed and the resulting solid
20 was triturated with ether/EtOAc. The tacky tan solid was filtered to afford III-6 as its bis-HCl salt.
1H NMR (CD₃OD) δ 8.85 (bt, 1H), 7.85 (d, J=9.5Hz, 1H), 6.95 (s, 1H), 6.83 (d, J=9.5Hz, 1H), 6.54 (s, 1H), 4.80 (s, 2H), 4.30 (bs, 2H), 3.80 (m, 1H), 2.50 (s, 3H), 2.40 (s, 3H), 1.40 (d, J=7.4 Hz, 6H).
30 Anal. Calc'd for C₁₈H₂₅N₅O₂S.2.55 CH₃OH.1.65HCl: C; 47.77, H; 7.19, N; 13.56. Found: C; 47.84, H; 7.18, N; 13.53.

EXAMPLE IV

Preparation of 3-Amino-4-cyclopropylmethylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone

5

IV-6Step A: 2-Cyclopropylmethylthiobenzothiazole (IV-1)

A stirred mixture of 2-mercaptobenzothiazole (1.67 g, 10.0 mmol), bromomethylcyclopropane (0.97 mL, 10.0 mmol) and sodium hydrogencarbonate (0.84 g, 10.0 mmol) in absolute ethanol (10 ml) was heated to reflux. After 8 h, the reaction was diluted with ethyl acetate and was washed with water, sodium carbonate solution and brine, dried (Na₂SO₄) and evaporated *in vacuo* to give IV-1 as an oil which was used without purification in the next step:

¹H NMR (300 Mz, CDCl₃) selected signals d 0.39 (m, 2H), 0.65 (m, 2H), 1.26 (m, 1H), 3.32 (d, J = 7.3 Hz, 2H).

Step B: 2-Cyclopropylmethylsulfonylbenzothiazole (IV-2)

A solution of potassium permanganate (1.90 g, 12.0 mmol) in water (100 mL) was added to a stirred solution of 2-cyclopropylmethylthiobenzothiazole (1.90 g) in acetic acid (150 mL). After 2 h, the dark brown mixture was decolorized with 10% sodium sulfite solution and water (500 mL) was added. The resulting precipitate was collected by filtration, washing with water, and dried at 0.5 mm Hg, to give IV-2 as a white crystalline solid.

¹H NMR (300 Mz, CDCl₃) selected signals d 0.28 (m, 2H), 0.64 (m, 2H), 1.21 (m, 1H), 3.46 (d, J = 7.3 Hz, 2H).

Step C: 4-Cyclopropylmethylsulfonyl-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (IV-3)

Sodium borohydride (113 mg, 3.0 mmol) was added in portions to a stirred mixture of 2-

- 5 cyclopropylmethylsulfonylbenzothiazole (0.38 g, 1.50 mmol) in absolute ethanol (3 mL) with cooling. After 2 h, glacial acetic acid was added dropwise to dissolve the suspension, giving a solution pH 4-5 (moist pH paper) and 4-chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (275 mg, 1.0 mmol) was added. The solid quickly dissolves
10 and then a thick precipitate forms. After 2 h the solids were collected by filtration, washing with ethanol, and dried at 0.5 mm Hg to give IV-3 as a bright yellow powder.

- ¹H NMR (CDCl₃) δ 0.40 (m, 2H), 0.70 (m, 2H), 1.13 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H), 2.46 (s, 3H), 3.33 (d, J = 7.3 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 4.88
15 (s, 2H), 6.62 (s, 1H)

Step D: 3-Amino-4-cyclopropylmethylsulfonyl-6-methyl-1-(ethyl-methylenecarboxy)-2-pyridinone (IV-4)

- A mixture of 4-cyclopropylmethylsulfonyl-6-methyl-3-nitro-
20 1-(ethyl-methylenecarboxy)-2-pyridinone (365 mg) and 10% palladium on carbon (0.30 g) in ethyl acetate (100 mL) was stirred under an atmosphere of hydrogen (balloon) for 3 h. The reaction mixture was filtered through celite, washing with ethyl acetate, and evaporated in vacuo to give IV-4 as a colorless crystalline solid which was used
25 without purification in the next step.

¹H NMR (CDCl₃) δ 0.27 (m, 2H), 0.63 (m, 2H), 1.08 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 2.23 (d, J = 0.9 Hz, 3H), 3.02 (d, J = 7.1 Hz, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.80 (s, 2H), 5.88 (br s, 2H), 6.28 (d, J = 0.9 Hz, 1H).

- 30 **Step E:** 3-Amino-4-cyclopropylmethylsulfonyl-6-methyl-1-methylenecarboxy-2-pyridinone (IV-5)

- Lithium hydroxide hydrate (84 mg, 2.0 mmol) was added to a stirred mixture of 3-amino-4-cyclopropylmethylsulfonyl-6-methyl-1-(ethyl-methylenecarboxy)-2-pyridinone (the product from Step D) in 2:2:1
35 methanol/THF/water (10 mL). After 2 h a thick white precipitate

formed. The mixture was acidified with 1 M HCl to give a clear solution which was partitioned between methylene chloride and brine. The brine was re-extracted with methylene chloride and the combined organic layers were dried (Na₂SO₄) and evaporated in vacuo to give a crystalline solid. This was heated to reflux as a suspension in methylene chloride (10 mL), cooled and the solids collected by filtration to give IV-5 as a colorless crystalline solid.

¹H NMR (d₆ DMSO) δ 0.25 (m, 2H), 0.50 (m, 2H), 0.92 (m, 1H), 2.20 (s, 3H), 3.18 (d, J = 7.1 Hz, 2H), 4.73 (s, 2H), 6.16 (br s, 2H), 6.20 (s, 1H).

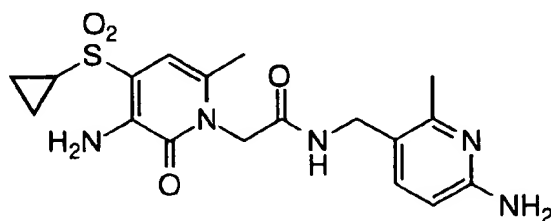
Step F: 3-Amino-4-cyclopropylmethylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (IV-6)

N-Methylmorpholine (0.187 mL, 1.70 mmol) was added to a stirred mixture of 3-amino-4-cyclopropylmethylsulfonyl-6-methyl-1-methylenecarboxy-2-pyridinone (120 mg, 0.40 mmol), 2-amino-5-aminomethyl-6-methylpyridine dihydrochloride (84 mg, 0.40 mmol), EDC.HCl (96 mg, 0.50 mmol) and HOBt.H₂O (68 mg, 0.50 mmol) in DMF (2 mL). After 16 h, water (20 mL) was added to give a white precipitate and after allowing to stand for 30 min, the solids were collected by filtration, washing with water, ethanol and ethyl acetate and air dried. 9.9 M HCl in absolute ethanol (0.1 mL) was added to a stirred fine suspension of the resulting white solid in absolute ethanol (5 mL) to give a solution. Over 1 h a pale yellow crystalline precipitate formed which was collected by filtration, washing with ethanol and dried at 0.5 mm Hg to give IV-6 as a pale peach colored crystalline solid.

¹H NMR (d₆ DMSO) δ 0.25 (m, 2H), 0.50 (m, 2H), 0.91 (m, 1H), 2.17 (s, 3H), 2.44 (s, 3H), 3.17 (d, J = 7.1 Hz, 2H), 4.16 (d, J = 5.6 Hz, 2H), 4.68 (s, 2H), 6.12 (br s, 2H), 6.18 (d, J = 0.7 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 7.63 (br s, 2H), 7.76 (d, J = 9.0 Hz, 1H), 8.72 (br t, J = 5.6 Hz, 1H); Anal. Calc. for C₁₉H₂₅N₅O₄S.HCl.2H₂O: C 46.38, H 6.15, N 14.24. Found: C 46.51, H 6.08, N 13.89.

EXAMPLE VPreparation of 3-Amino-4-cyclopropylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone

5

V-3Step A: Lithium cyclopropylsulfinate (V-1)

V-1 was prepared by a modification of the method of Crowell
 10 *et. al.* (*J. Med. Chem.* 1989, 32, 2436). A solution of cyclopropyl bromide
 (1.73 mL, 21.6 mmol) in dry diethyl ether (4 mL) was added dropwise to a
 stirred slurry of 30% lithium dispersion in mineral oil (1.0 g) in dry
 ether (8 mL) at 0° C (internal T < 5° C) under nitrogen. After 3 h, an
 excess of sulfur dioxide was blown on to the surface of the mixture to
 15 give a thick white precipitate. The solvent was evaporated in vacuo and
 absolute ethanol (50 mL) was added cautiously. The resulting mixture
 was stirred thoroughly and filtered, washing with ethanol. The filtrate
 was evaporated in vacuo to give V-1 which was used without purification
 in the next step:

20 ¹H NMR (CD₃OD) δ 0.61 (m, 2H), 0.75 (m, 2H), 1.87 (m, 1H).

Step B: 4-Cyclopropylsulfonyl-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (V-2)

Glacial acetic acid was added dropwise to a solution of the
 25 crude lithium cyclopropylsulfinate from Step A (448 mg) in absolute
 ethanol (2 mL) to give a solution pH 4-5 (moist pH paper). 4-Chloro-6-
 methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (137 mg, 0.50
 mmol) was added to give solution. Over 1 h a thick precipitate forms
 which was collected by filtration, washing with ethanol, and dried at 0.5

mm Hg to give V-2 as a yellow solid which was used without purification in the next step.

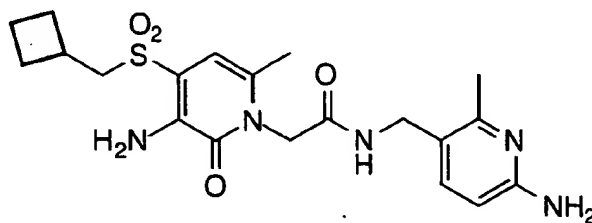
Step C: 3-Amino-4-cyclopropylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (V-3)

V-3 was prepared from 4-cyclopropylsulfonyl-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone using the procedures of Example IV, Steps D - F.

¹H NMR (d6 DMSO) δ 1.04 (m, 2H), 1.11 (m, 2H), 2.17 (s, 3H), 2.44 (s, 3H), 2.88 (m, 1H), 4.16 (d, J = 5.5 Hz, 2H), 4.67 (s, 2H), 6.09 (br s, 2H), 6.18 (d, J = 0.6 Hz, 1H), 6.80 (d, J = 9.0 Hz, 1H), 7.65 (br s, 2H), 7.77 (d, J = 9.0 Hz, 1H), 8.75 (br t, J = 5.5 Hz, 1H); Anal. Calc. for C₁₈H₂₃N₅O₄S.HCl.0.3H₂O: C 48.32, H 5.54, N 15.66. Found: C 48.41, H 5.38, N 15.28.

EXAMPLE VI

Preparation of 3-Amino-4-cyclobutylmethylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone



VI-1

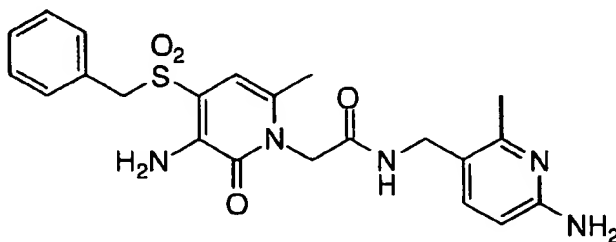
VI-1 was prepared from bromomethylcyclobutane using the procedures of Example IV, Steps A - F.

¹H NMR (d6 DMSO) δ 1.76-2.01 (m, 6H), 2.16 (s, 3H), 2.44 (s, 3H), 2.60 (m, 1H), 3.35 (d, J = 7.1 Hz, 2H), 4.16 (d, J = 5.1 Hz, 2H), 4.67 (s, 2H), 6.10 (br s, 2H), 6.15 (s, 1H), 6.80 (d, J = 9.0 Hz, 1H), 7.66 (br s, 2H), 7.76 (d, J = 9.0 Hz, 1H), 8.73 (br t, 1H).

EXAMPLE VII

Preparation of 3-Amino-4-benzylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone

5



VII-2

a) VII-2 was prepared from benzyl bromide using the procedures of Example IV, Steps A - F.

10 ^1H NMR (d6 DMSO) δ 2.14 (s, 3H), 2.24 (d, $J = 1.1$ Hz, 3H), 4.12 (d, $J = 4.8$ Hz, 2H), 4.54 (s, 2H), 4.67 (s, 2H), 5.72 (s, 2H), 6.05 (br s, 3H), 6.23 (d, $J = 8.2$ Hz, 1H), 7.21 (d, $J = 8.2$ Hz, 1H), 7.27-7.34 (m, 5H), 8.43 (br t, 1H).

b) Alternatively, VII-2 may be prepared from 4-benzylthio-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone by oxidation with OXONE® to give 4-benzylsulfonyl-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (VII-1), followed by the use of the procedures of Example IV, Steps D-F:

20 Preparation of 4-Benzylsulfonyl-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (VII-1)

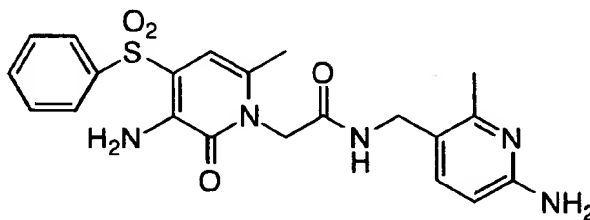
A mixture of 4-benzylthio-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (135 mg, 0.373 mmol) and OXONE® (688 mg, 1.12 mmol) in 1:1 methanol/water (3 mL) was stirred for 9
25 days. The mixture was partitioned between ethyl acetate and water and the organic layer was washed with 5% sodium metabisulfite solution and brine, dried (Na_2SO_4) and evaporated in vacuo to an oil. The crude product was purified by flash column chromatography on silica (70% ethyl acetate/hexanes) to give VII-1.

¹H NMR (CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 4.27 (q, J = 7.1 Hz, 2H), 4.62 (s, 2H), 4.81 (s, 2H), 6.00 (s, 1H), 7.36 (s, 5H).

EXAMPLE VIII

5

Preparation of 3-Amino-4-phenylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone



VIII-2

10

Step A: 6-Methyl-3-nitro-4-phenylsulfonyl-1-(ethyl-methylenecarboxy)-2-pyridinone (VIII-1)

4-Chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone (100 mg, 0.40 mmol) was added to a stirred solution of sodium benzene sulfinate (66 mg, 0.40 mmol) in DMF (0.40 ml). After 2 h the mixture was partitioned between water and ethyl acetate. The organic layer was dried (Na₂SO₄) and evaporated in vacuo to a yellow gum which was purified by flash column chromatography (ethyl acetate/hexanes gradient, 40-70% ethyl acetate) to give VIII-1 as a yellow gum.

20

¹H NMR (CD₃OD) δ 1.26 (t, J = 7.1 Hz, 3H), 2.46 (s, 3H), 4.22 (q, J = 7.1 Hz, 2H), 4.90 (s, 2H), 6.80 (s, 1H), 7.66-8.05 (m, 5H).

Step B: 3-Amino-4-phenylsulfonyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (VIII-2)

25

VIII-2 was prepared, as the free base, from 6-methyl-3-nitro-4-phenylsulfonyl-1-(ethyl-methylenecarboxy)-2-pyridinone using the procedures of Example IV, Steps D - F.

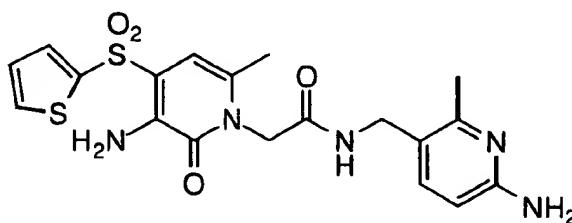
¹H NMR (d6 DMSO) δ 2.15 (s, 3H), 2.42 (s, 3H), 4.13 (d, J = 5.7 Hz, 2H), 4.62 (s, 2H), 6.29 (s, 1H), 6.32 (s, 2H), 6.79 (d, J = 9.0 Hz, 1H), 7.24 (t, J = 4.4 Hz, 1H), 7.67 (br s, 2H), 7.74 (d, J = 9.0 Hz, 1H), 7.94 (dd, J = 0.6 and 3.7 Hz, 1H), 8.07 (dd, J = 0.6 and 4.9 Hz, 1H), 8.41 (br t, 1H).

5

EXAMPLE IX

Preparation of 3-Amino-4-(2-thienylsulfonyl)-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone

10



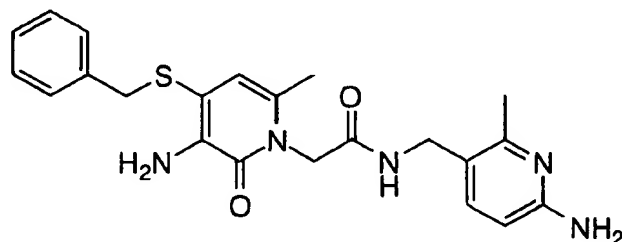
IX-1

IX-1 was prepared as the HCl salt from 4-chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone and sodium thienylsulfinate [which was prepared by the method of Crowell *et. al.* (*J. Med. Chem.* 1989, 32, 2436)] using the procedure of Example VIII.

15

¹H NMR (d6 DMSO) δ 2.14 (s, 3H), 2.20 (s, 3H), 4.08 (d, J = 4.9 Hz, 2H), 4.60 (s, 2H), 5.70 (s, 2H), 6.21 (d, J = 8.2 Hz, 1H), 6.29 (s, 1H), 6.30 (s, 2H), 7.17 (d, J = 8.2 Hz, 1H), 7.62-7.99 (m, 5H), 8.41 (br t, 1H).

20

EXAMPLE XPreparation of 3-Amino-4-benzylthio-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinoneX-2

5

Step A: 3-Amino-4-benzylthio-6-methyl-1-(ethyl-methylenecarboxy)-2-pyridinone (X-1)

Iron powder (39 mg) was added to a stirred solution of 4-benzylthio-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone [prepared from benzyl mercaptan and 4-chloro-6-methyl-3-nitro-1-(ethyl-methylenecarboxy)-2-pyridinone using the procedure of Example III, Step B] in a mixture of acetic acid (1.1 mL) and water (0.2 mL) and the resulting mixture was heated to 90° C. After 4 h, the mixture was cooled and filtered, washing with acetic acid. The filtrate was partitioned between ethyl acetate and water and the organic layer was washed with water, dried (Na₂SO₄) and evaporated in vacuo to an oil. The crude product was purified by flash column chromatography on silica (30% ethyl acetate/hexanes) to give X-1 as an oil.

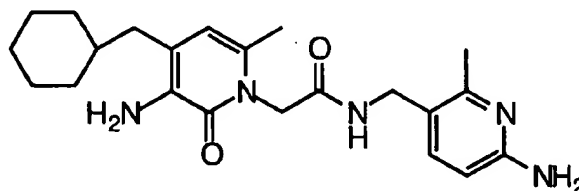
¹H NMR (CDCl₃) δ 1.28 (t, J = 7.3 Hz, 3H), 2.16 (s, 3H), 4.00 (s, 2H), 4.24 (q, J = 7.3 Hz, 2H), 4.46 (br s, 2H), 4.78 (s, 2H), 5.98 (s, 1H), 7.26 (m, 5H).

Step B: 3-Amino-4-benzylthio-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (X-2)

- X-2 was prepared, as the free base, from 3-amino-4-benzylthio-6-methyl-1-(ethyl-methylenecarboxy)-2-pyridinone using the procedures of Example IV, Steps E and F.
MS (FAB) 424 (M+1)+.

EXAMPLE XI

- 10 Preparation of 3-Carboxymethylamino-4-cyclohexylmethyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone



XI-7

- 15 Step A: 1-(t-Butyl methylenecarboxy)-6-Methyl-3-nitropyridin[1H]-2-one (XI-1)

- To a 0°C stirred suspension of 1.0 g (6.49 mmol) of 6-methyl-3-nitropyridin-2-one in 15 mL anhydrous DMF under Ar was added 262 mg (6.55 mmol) of NaH (60% in mineral oil) in 3 portions.
20 After the mixture became homogeneous over 15 min, 1.06 mL (6.55 mmol) of t-butyl bromoacetate was in two portions. The cold bath was removed and the reaction mixture stirred under Ar overnight. An additional portion of 0.2 mL of t-butyl bromoacetate was added, and the reaction heated to 50°C for 17 h. Concentration of the reaction
25 mixture at reduced pressure gave a residue that was partitioned between ethyl acetate and 1M citric acid. The aq. layer was extracted with ethyl acetate, and the combined organic layers washed with 10% Na₂CO₃, brine, treated with activated carbon, dried over Na₂SO₄, and the solvents removed to give an oil that was chromatographed on

12 g of SiO₂ using 1:2 to 1:1 EtOAc-hexanes which gave XI-1 as a yellow solid:

¹H NMR (CDCl₃) δ 8.34 (d, 1H, 8.0 Hz), 6.20 (d, 1H, 7.8 Hz), 4.81 (s, 2H), 2.43 (s, 3H), 1.49 (s, 9H).

5

Step B: 1-(t-Butyl methylenecarboxy)-4-cyclohexylmethyl-3,4-dihydro-6-methyl-3-nitro-pyridin[1H]-2-one (XI-2)

To a stirred suspension of 73 mg (3.0 mmol) of Mg turnings and a small crystal of I₂ in 3 mL of dry THF was added 349
10 μL (2.5 mmol) of bromomethylcyclohexane, and the mixture heated to reflux for 2h as the Mg slowly dissolved. After cooling to ambient temperature, the resulting solution was added dropwise via syringe to a -78°C stirred solution of 537 mg (2.0 mmol) 1-(t-butyl
15 methylenecarboxy)-6-methyl-3-nitro-pyridin[1H]-2-one in 6 mL of dry THF. After stirring in the cold for 45 min, the cold bath was removed and, as the reaction reached -15°C, it was quenched by the dropwise addition of 286 μL (5 mmol) of acetic acid. After removal of the solvents at reduced pressure, the residue was partitioned between EtOAc and cold 5% HCl. The organic layer was washed with 5%
20 NaHCO₃, brine, dried over Na₂SO₄ and the solvents removed to give a yellow oil that was chromatographed on 50 g of SiO₂ using 1:3 EtOAc-hexane to give XI-2 as a yellow semi-solid:

¹H NMR (CDCl₃) δ 4.97-5.0 (m, 2H), 4.42 (d, 1H, 17.6 Hz), 4.21 (d, 2H, 17.7 Hz), 3.25-3.35 (m, 1H), 1.89 (t, 3H, 1.5 Hz), 1.60-1.80 (m, 6H), 1.49
25 (s, 9H), 1.03-1.48 (m, 11 H), 0.8-1.02 (m, 2H).

Step C: 1-(t-Butyl methylenecarboxy)-4-cyclohexylmethyl-6-methyl-3-nitro-pyridin[1H]-2-one (XI-3)

To a stirred suspension of 104 mg of nickel peroxide
30 hydrate in 5 mL of CHCl₃ was added 126 mg (0.34 mmol) of 1-(t-butyl methylenecarboxy)-4-cyclohexylmethyl-3,4-dihydro-6-methyl-3-nitro-pyridin[1H]-2-one. After 2h, an additional 127 mg of nickel peroxide hydrate was added, and the mixture stirred for another 2h. Filtration and concentration of the filtrate at reduced pressure gave

XI-3 as a yellow oil: ^1H NMR (CDCl_3) δ 5.95 (s, 1H), 4.74 (s, 2H), 2.37 (d, 1H, 7.1 Hz), 2.31 (s, 3H), 1.52-1.80 (m, 6H), 1.48 (s, 9H), 1.03-1.30 (m, 8 H), 0.85-1.02 (m, 3H).

5 Step D: 1-Methylenecarboxy-4-cyclohexylmethyl-6-methyl-3-nitro-pyridin[1H]-2-one (XI-4)

To a stirred solution of 120 mg (0.33 mmol) of 1-(t-butyl methylenecarboxy)-4-cyclohexylmethyl-6-methyl-3-nitro-pyridin[1H]-2-one in 7.5 mL of CH_2Cl_2 was added 7.5 mL of TFA and stirred
10 under Ar for 1h. The solvents were removed at reduced pressure, and the residue partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc and the combined organic layers washed with brine, treated with activated carbon, dried over Na_2SO_4 and solvents removed to give XI-4 as a light tan solid which was
15 carried forward to the next step.

Step E: 4-Cyclohexylmethyl-6-methyl-3-nitro-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyridin[1H]-2-one (XI-5)

The product from Step C was dissolved in 3 mL of DMF along with 44 mg (0.32 mmol) of 1-hydroxybenzotriazole and 77 mg (0.32 mmol) of 2-t-butylloxycarbonylamino-5-aminomethyl-6-methylpyridine. To this stirred solution was added 62 mg (0.32
25 mmol) of EDC and 90 μL (0.65 mmol) of triethylamine, and stirred under Ar overnight. The solvents were removed at reduced pressure, and the residue partitioned between EtOAc and 1M citric acid. The aqueous layer was extracted with EtOAc, and the combined organic layers washed with 10% Na_2CO_3 , brine, treated with activated
30 carbon, dried over Na_2SO_4 and the solvents removed at reduced pressure to give XI-5 as a yellow oil which was carried forward to the next step.

Step F: 3-Amino-4-cyclohexylmethyl-6-methyl-1-(2-t-butylloxycarbonylamino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-pyridin[1H]-2-one (XI-6)

5 The product from Step D was dissolved in 18 mL of ethanol, 2 mL of water, 1 mL of acetic acid and hydrogenated at 50 psi using 32 mg of 20% Pd(OH)₂ on carbon overnight. The catalyst was removed by filtration, concentrated at reduced pressure and the residue partitioned between CHCl₃ and 10% Na₂CO₃. The organic
10 layer was dried over Na₂SO₄ and the solvents removed at reduced pressure to give XI-6 as a yellow oil:

¹H NMR (CDCl₃) δ 7.64 (d, 1H, 8.3 Hz), 7.38 (d, 1H, 8.4 Hz), 7.36 (br t, 1H), 7.12 (br s, 1H), 5.88 (s, 1H), 4.73 (s, 2H), 4.33 (d, 2H, 5.7 Hz), 3.93 (s, 2H), 2.37 (s, 3H), 2.34 (s, 3H), 2.24 (d, 7.1 Hz), 1.51-1.75 (m, 7H), 1.50
15 (s, 9H), 1.05-1.28 (m, 4H), 0.92-1.05 (m, 2H).

Step G: 3-Amino-4-cyclohexylmethyl-6-methyl-1-(2-amino-6-methyl-5-methylenecarboxamidomethylpyridinyl)-2-pyridinone (XI-7)

20 The product from Step F was dissolved in 5 mL of CH₂Cl₂ and treated with 5 mL of TFA under Ar for 1h, concentrated at reduced pressure and purified by gradient elution preparative HPLC using a C-18 stationary phase and 0.1% aqueous TFA/CH₃CN as the mobile phase. The fractions were assayed by analytical HPLC, combined and
25 concentrated at reduced pressure and lyophilized to provide XI-7 as a colorless solid: ¹H NMR (D₆-DMSO) δ 8.68 (br t, 1H), 7.78 (d, 1H, 9.1 Hz), 7.74 (br s, 2H), 6.80 (d, 1H, 8.8 Hz), 5.91 (s, 1H), 4.66 (s, 2H), 4.15 (br d, 2H), 2.43 (s, 3H), 2.20-2.40 (m, 5 H), 2.16 (s, 3H), 1.50-1.70 (m, 6 H), 1.05-1.25 (m, 3H), 0.9-1.05 (m, 2H).

30

EXAMPLE XIITablet Preparation

5 Tablets containing 10.0, 25.0, and 50.0 mg, respectively, of
compound VII-2 are prepared as illustrated below:

	<u>Ingredient</u>	<u>Amount-mg</u>		
		10.0	25.0	50.0
10	VII-2	10.0	25.0	50.0
	Microcrystalline cellulose	80.0	100.0	150.0
	Modified food corn starch	10.0	15.0	20.0
15	Magnesium stearate	0.75	1.0	1.5

20 All of the active compound, cellulose, and a portion of the
corn starch are mixed and granulated to 10% corn starch paste. The
resulting granulation is sieved, dried and blended with the remainder of
the corn starch and the magnesium stearate. The resulting granulation
is then compressed into tablets containing 10.0, 25.0, and 50.0 mg,
respectively, of active ingredient per tablet.

EXAMPLE XIII

An intravenous dosage form of the above-indicated active compound is prepared as follows:

5	VII-2	0.5-10.0mg
	Sodium Citrate	5-50mg
10	Citric Acid	1-15mg
	Sodium Chloride	1-8mg
	Water for Injection (USP)	q.s. to 1 L

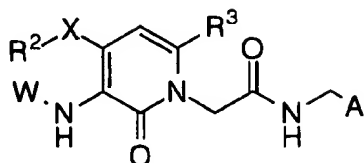
15

Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland, copyright 1994.

20

WHAT IS CLAIMED IS:

1. A compound having the following structure:



5 wherein

W is

hydrogen,

R¹-,

R¹OC(O)-,

10 R¹C(O)-,

R¹SO₂-,

(R¹)_m(CH₂)_nNH_qC(O)-,

where n is 0-4, m is 1 or 2, wherein R¹ is same or different, and

q is 0 or 1, with the proviso that where n is 1-4, q is 1 and m is 1,

15 and where n is 0, m is 1 or 2, and q is 0 or 1, and where n is 0,

m is 2 and q is 0;

R¹ is

R¹⁷(CH₂)_t, where t is 0-4;

20 (R¹⁷)(OR¹⁷)CH(CH₂)_p-, where p is 1-4,

(R¹⁷)₂CH(CH₂)_r-, where r is 0-4 and each R¹⁷ can be the same or

different, and wherein (R¹⁷)₂ can also form a ring with CH

represented by C₃₋₇ cycloalkyl, C₇₋₁₂ bicyclic alkyl, C₁₀₋₁₆

tricyclic alkyl, or a 5- to 7- membered mono- or bicyclic

25 heterocyclic ring which can be saturated or unsaturated, and

which contains from one to three heteroatoms selected from

the group consisting of N, O and S,

R¹⁷O(CH₂)_p-, wherein p is 1-4;

30 R², R¹⁴ and R¹⁷ are independently selected from

- phenyl, unsubstituted or substituted with one or more of
C₁₋₄ alkyl,
C₁₋₄ alkoxy,
halogen,
5 hydroxy,
COOH, or
CONH₂,
naphthyl,
biphenyl,
10 a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
group consisting of N, O and S,
-C₁₋₇ alkyl, unsubstituted or substituted with one or more of
15 hydroxy,
COOH,
amino,
aryl,
C₃₋₇ cycloalkyl,
20 heteroaryl, or
heterocycloalkyl,
-CF₃
C₃₋₇ cycloalkyl,
C₇₋₁₂ bicyclic alkyl, or
25 C₁₀₋₁₆ tricyclic alkyl;

X is

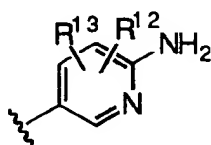
- CF₂,
30 CR¹⁵,R¹⁶
wherein R¹⁵ and R¹⁶ are independently
hydrogen,
C₃₋₇ cycloalkyl,
C₁₋₄ alkyl unsubstituted or substituted with one or more of
35 hydroxy,

COOH,
 amino,
 aryl,
 heteroaryl, or
 heterocycloalkyl,
 aryl,
 heteroaryl,
 heterocycloalkyl, or
 R¹⁵ and R¹⁶ are joined to form a four to seven
 membered cycloalkyl ring unsubstituted or
 substituted with hydroxy, amino or aryl, or

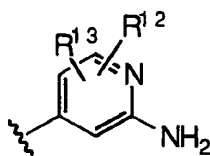
S(O)_r, where r is 0-2;

R³ is
 hydrogen,
 C₁₋₄ alkyl,
 C₃₋₇ cycloalkyl, or
 trifluoromethyl;

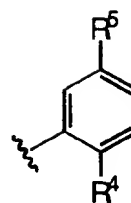
A is chosen from one of the following radicals:



II



III



IV

with the proviso that when A is radical IV, R²-X is not C₁₋₄ alkyl,
 C₃₋₇ cycloalkyl, or trifluoromethyl;

R⁴ is
 hydrogen,

- C₁₋₄ alkyl,
C₁₋₄ alkoxy,
halogen,
-OCH₂CF₃,
5 -COOH,
-OH,
-COOR⁶, where R⁶ is C₁₋₄alkyl,
-CONR⁷R⁸, where R⁷ and R⁸ are independently
hydrogen or C₁₋₄alkyl,
10 -(CH₂)₁₋₄OH,
-CH₂NHC(O)CH₃,
-CH₂NHC(O)CF₃,
-CH₂NHSO₂CH₃,
-SO₂NH₂,
15 -(CH₂)₁₋₄SO₂NR⁷R⁸,
-(CH₂)₁₋₄SO₂R⁶,
a 5- to 7- membered mono- or a 9- to 10-membered bicyclic
heterocyclic ring which can be saturated or unsaturated, and
which contains from one to four heteroatoms selected from the
20 group consisting of N, O and S,
-ZCH₂CO₂H,
-ZCH₂CO₂CH₃,
-ZCH₂R¹⁴,
-ZCH₂CO₂(CH₂)₁₋₃CH₃,
25 -Z(CHR⁹)₁₋₃C(O)NR¹⁰R¹¹,
wherein
R⁹ is H or C₁₋₄ alkyl,
R¹⁰ and R¹¹ are independently
hydrogen,
30 C₃₋₇ cycloalkyl,
aryl,
heteroaryl,
heterocycloalkyl,
C₁₋₄ alkyl unsubstituted or substituted with one or more of
35 hydroxy,

COOH,
 amino,
 aryl,
 heteroaryl, or
 heterocycloalkyl, or
 R¹⁰ and R¹¹ are joined to form a four to seven
 membered cycloalkyl ring unsubstituted or
 substituted with hydroxy, amino or aryl,

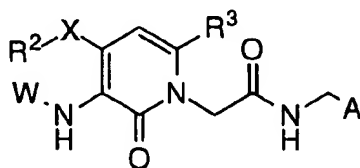
wherein Z is O, S or CH₂;

R⁵ is
 hydrogen,
 halogen,
 C₁₋₄ alkyl,
 C₁₋₄ alkoxy,
 CN, or
 CO₂NH₂; and

R¹² and R¹³ are independently
 hydrogen,
 C₁₋₄ linear or branched alkyl or alkoxy,
 C₃₋₇ cycloalkyl,
 halogen, or
 trifluoromethyl;

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1 having the formula:



wherein

W is

- hydrogen,
- C₁₋₄ alkyl,
- C₃₋₇cycloalkyl,
- 5 -SO₂C₁₋₇ alkyl, or
- (CH₂)_nCOOH, where n is 1-4;

R² is

- 10 -C₁₋₇ alkyl
- (CH₂)_u-C₃₋₇cycloalkyl, wherein u is 0, 1, or 2,
- (CH₂)_u-phenyl, wherein phenyl is unsubstituted or substituted
with one or more of the moieties selected from the group
consisting of
- 15 C₁₋₄ alkyl,
- C₁₋₄ alkoxy,
- halogen,
- hydroxy,
- COOH, or
- 20 CONH₂
- wherein u is 0, 1, or 2,
- 2-thienyl, or
- 3-thienyl;

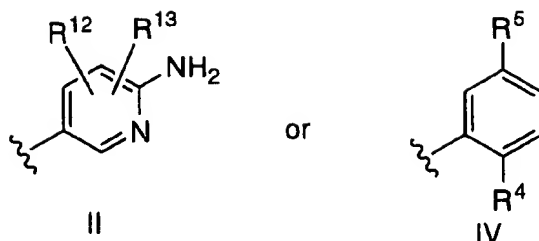
X is

- 25 -S-, -SO₂-, or CH₂;

R³ is

- C₁₋₄ linear alkyl;

- 30 A is chosen from one of the following radicals:

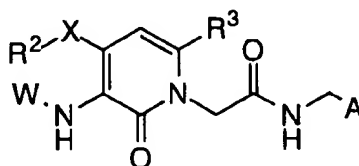


with the proviso that when A is radical IV, R²-X- is not C₁₋₄ alkyl,

and pharmaceutically acceptable salts thereof.

5

3. The compound of claim 2 having the formula:



wherein

W is

10 hydrogen,
 -SO₂CH₃, or
 -CH₃,
 -CH₂COOH;

15 R² is

 -CH₃,
 -(CH₂)_u-C₃₋₆cycloalkyl, wherein u is 0 or 1;
 -(CH₂)_u-phenyl, wherein u is 0 or 1,
 -CH₂C(CH₃)₃,
20 -CH(CH₃)₂,
 -phenyl-CH₃,
 -2-thienyl, or
 -3-thienyl;

25 X is

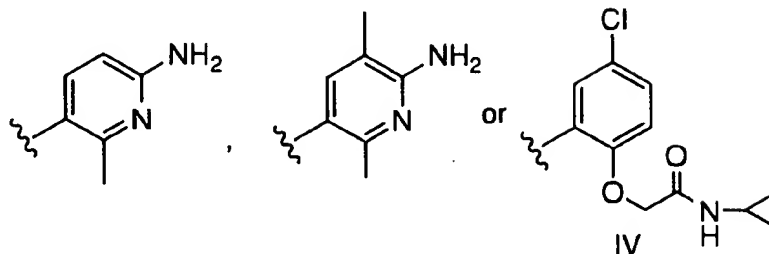
-S-, -SO₂-, or CH₂;

R³ is

-CH₃;

5

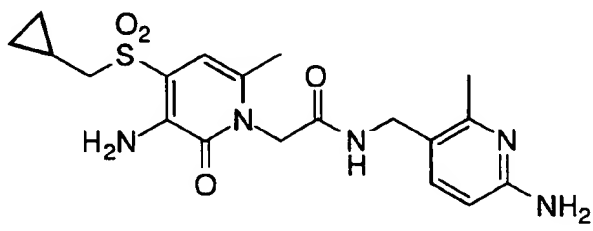
A is chosen from one of the following radicals:



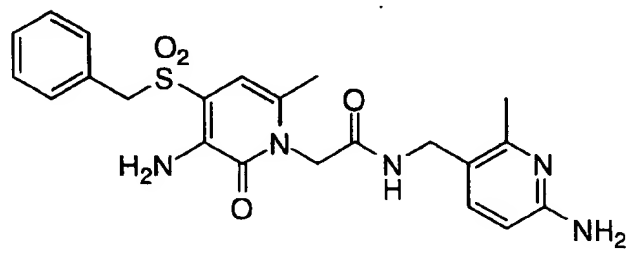
with the proviso that when A is radical IV, R²-X- is not C₁₋₄ alkyl,

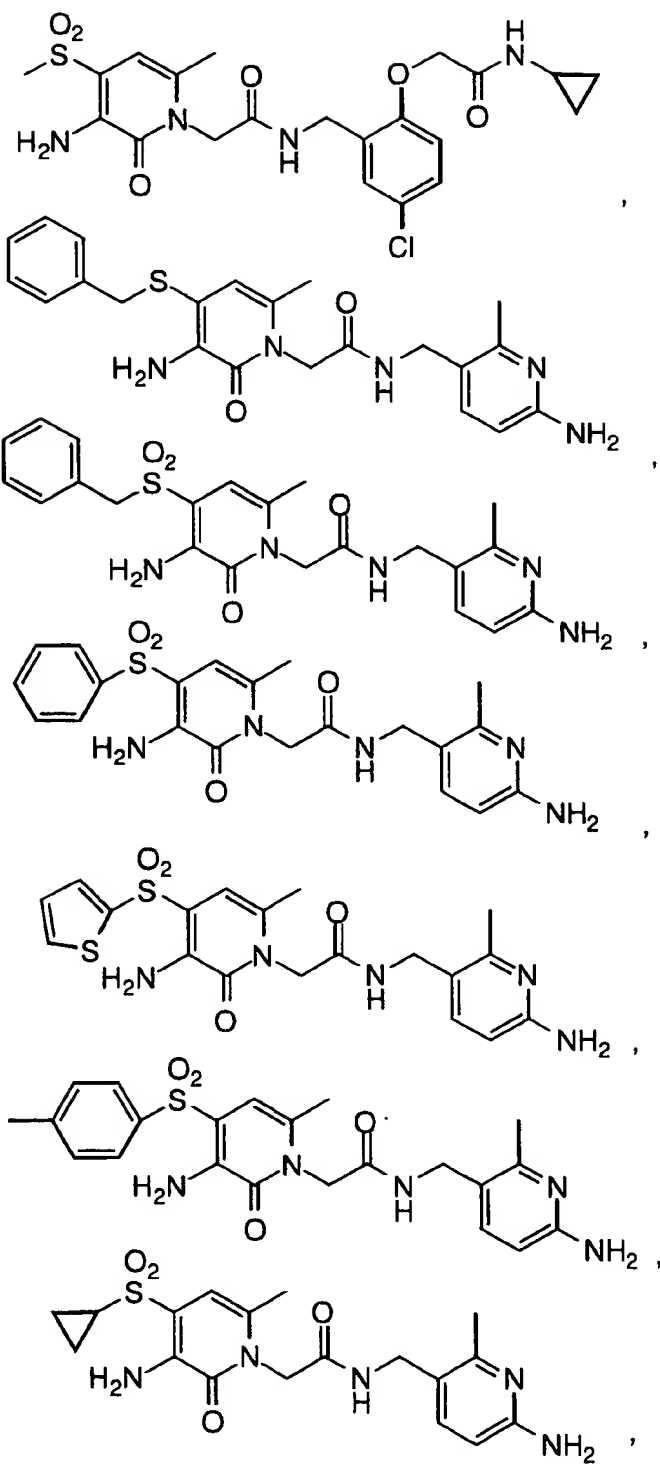
10 and pharmaceutically acceptable salts thereof.

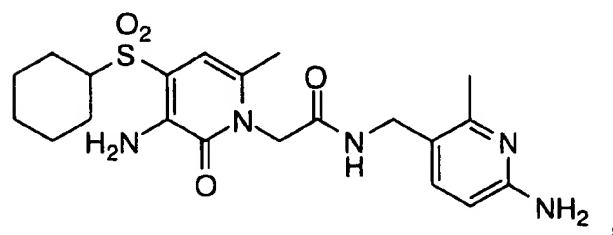
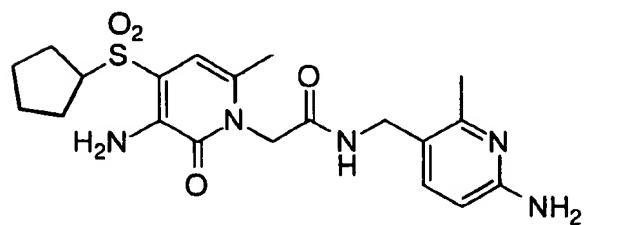
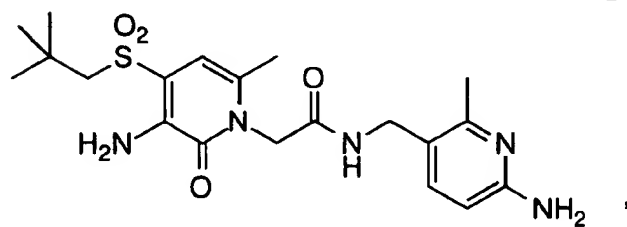
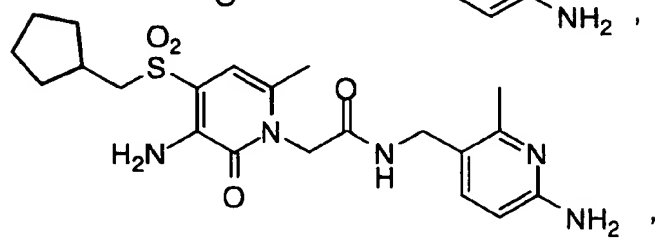
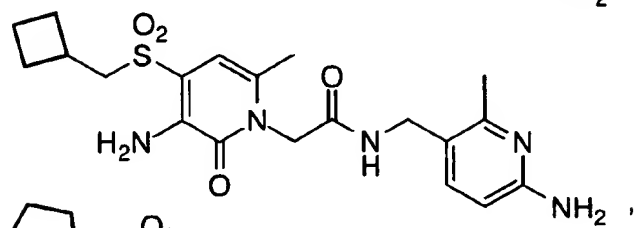
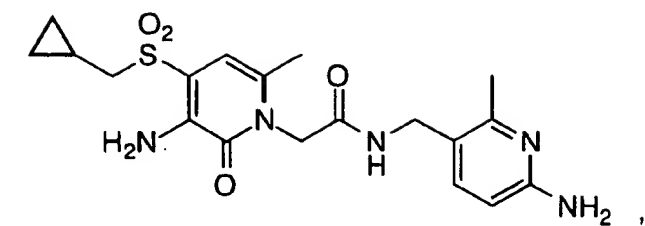
4. The compound of Claim 3 selected from the group consisting of:

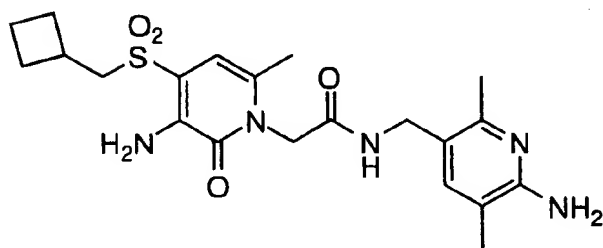
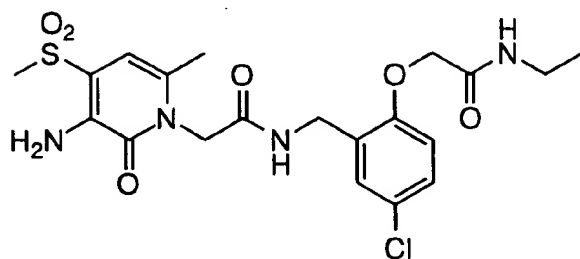
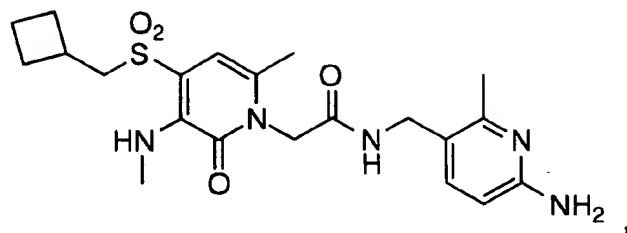


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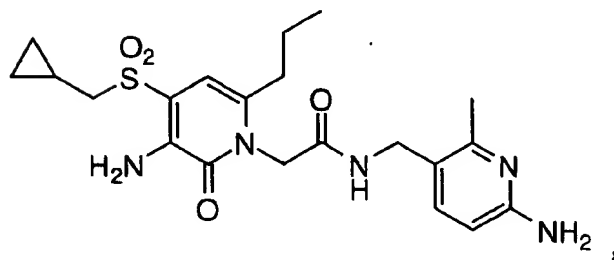


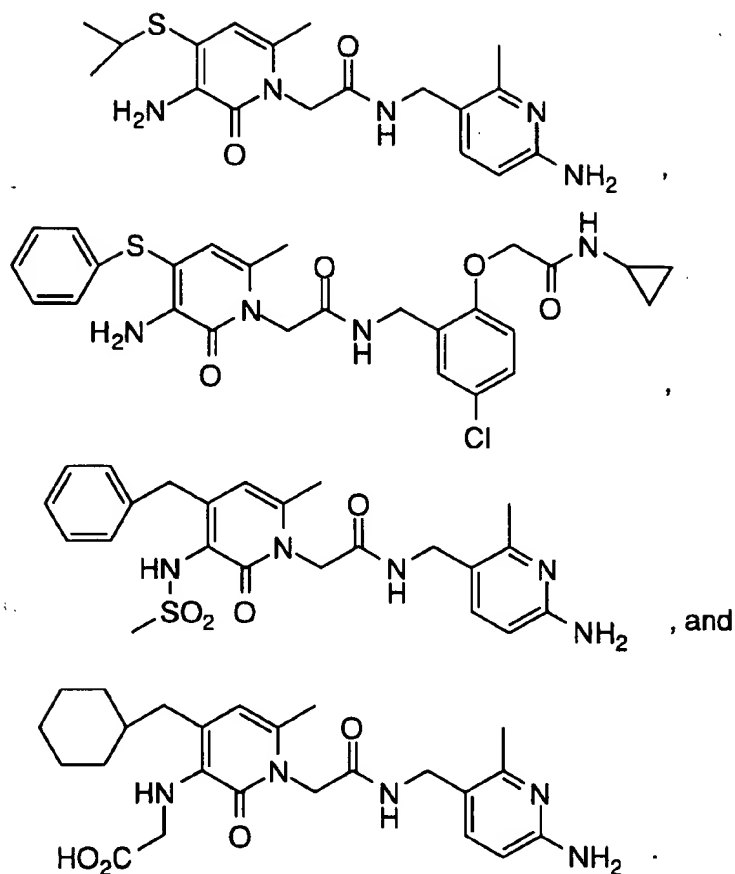






5





and pharmaceutically acceptable salts thereof.

5. A composition for inhibiting thrombin in blood comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

6. A method for inhibiting thrombin in blood in a mammal comprising administering to the mammal a composition of Claim 5.

7. A method for inhibiting formation of blood platelet aggregates in blood in a mammal comprising administering to the mammal a composition of Claim 5.

15

8. A method for inhibiting formation of fibrin in blood in a mammal comprising administering to the mammal a composition of Claim 5.

5 9. A method for inhibiting thrombus formation in blood in a mammal comprising administering to the mammal a composition of Claim 5.

10 10. A method for inhibiting thrombin in stored blood comprising administering to the mammal a composition of Claim 5.

15 11. A method for treating atrial fibrillation, deep venous thrombosis, pulmonary embolism, cardiac thromboembolism and associated stroke in patients with atrial fibrillation, mechanical heart valves, or recent myocardial infarction with decreased left ventricular function in a mammal comprising administering to the mammal a composition of Claim 5.

20 12. A method for preventing atrial fibrillation, deep venous thrombosis, pulmonary embolism, cardiac thromboembolism and associated stroke in patients with atrial fibrillation, mechanical heart valves, or recent myocardial infarction with decreased left ventricular function in a mammal comprising administering to the mammal a composition of Claim 5.

25 13. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting thrombus formation, preventing thrombus formation, inhibiting thrombin, inhibiting formation of fibrin, and 30 inhibiting formation of blood platelet aggregates, in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/00875

A. CLASSIFICATION F SUBJECT MATTER

IPC(6) : C07D 211/80, 401/02; A61K 31/44

US CL : 546/255, 297; 514/332, 349

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/255, 297; 514/332, 349

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS COMPUTER SEARCH 1966- TO DATE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/33974 A1 (THE GREEN CROSS CORPORATION) 31 October 1996, see entire document.	1-13



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A	document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means		
P document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

23 MARCH 1998

Date of mailing of the international search report

16 JUN 1998

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